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Screening for Colorectal Cancer
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Colorectal cancer (CRC) remains a significant cause of morbidity and mortality in the US.

OBJECTIVE To systematically review the effectiveness, test accuracy, and harms of screening for CRC to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant studies published from January 1, 2015, to December 4, 2019; surveillance through March 26, 2021.

STUDY SELECTION English-language studies conducted in asymptomatic populations at general risk of CRC.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently appraised the articles and extracted relevant study data from fair- or good-quality studies. Random-effects meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES Colorectal cancer incidence and mortality, test accuracy in detecting cancers or adenomas, and serious adverse events.

RESULTS The review included 33 studies (n = 10 776 276) on the effectiveness of screening, 59 (n = 3 491 045) on the test performance of screening tests, and 131 (n = 26 987 366) on the harms of screening. In randomized clinical trials (4 trials, n = 458 002), intention to screen with 1- or 2-time flexible sigmoidoscopy vs no screening was associated with a decrease in CRC-specific mortality (incidence rate ratio, 0.74 [95% CI, 0.68-0.80]). Annual or biennial guaiac fecal occult blood test (gFOBT) vs no screening (5 trials, n = 419 966) was associated with a reduction of CRC-specific mortality after 2 to 9 rounds of screening (relative risk at 19.5 years, 0.91 [95% CI, 0.84-0.98]; relative risk at 30 years, 0.78 [95% CI, 0.65-0.93]). In observational studies, receipt of screening colonoscopy (2 studies, n = 436 927) or fecal immunochemical test (FIT) (1 study, n = 5.4 million) vs no screening was associated with lower risk of CRC incidence or mortality. Nine studies (n = 6497) evaluated the test accuracy of screening computed tomography (CT) colonography, 4 of which also reported the test accuracy of colonoscopy; pooled sensitivity to detect adenomas 6 mm or larger was similar between CT colonography with bowel prep (0.86) and colonoscopy (0.89). In pooled values, commonly evaluated FITs (14 studies, n = 45 403) (sensitivity, 0.74; specificity, 0.94) and stool DNA with FIT (4 studies, n = 12 424) (sensitivity, 0.93; specificity, 0.85) performed better than high-sensitivity gFOBT (2 studies, n = 3503) (sensitivity, 0.50-0.75; specificity, 0.96-0.98) to detect cancers. Serious harms of screening colonoscopy included perforations (3.1/10 000 procedures) and major bleeding (14.6/10 000 procedures). CT colonography may have harms resulting from low-dose ionizing radiation. It is unclear if detection of extracolonic findings on CT colonography is a net benefit or harm.

CONCLUSIONS AND RELEVANCE There are several options to screen for colorectal cancer, each with a different level of evidence demonstrating its ability to reduce cancer mortality, its ability to detect cancer or precursor lesions, and its risk of harms.

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Although the incidence of colorectal cancer (CRC) has declined over time, it remains a significant cause of morbidity and mortality in the US. Among all cancers, it is third in incidence and cause of cancer death for both men and women.[1] In addition, cohort trends indicate that CRC incidence is decreasing only for persons 55 years or older.[2] From the mid-1990s until 2013 the incidence of CRC had increased annually by 0.5% to 1.3% in adults aged 40 to 54 years.[2]

In 2016, the US Preventive Services Task Force (USPSTF) recommended screening for CRC starting at age 50 years and continuing until age 75 years (A recommendation). The task force recommended that the decision to screen for CRC in adults aged 76 to 85 years should be based on the individual, accounting for the patient's overall health and prior screening history (C recommendation).[3] To complete screening, this recommendation offered a number of stool-based and direct visualization tests.

This systematic review was conducted to update the previous review[4,5] on the effectiveness, test accuracy, and harms of CRC screening as well as to inform a separate modeling report,[6,7] which together were used by the USPSTF in the process of updating its CRC screening recommendation.

Methods

Scope of Review

This review addressed 3 key questions (KQs), which are listed in **Figure 1**. No major changes were made to the scope of the previous review for the conduct of the current review except for the addition of 2 screening modalities (ie, capsule endoscopy, urine testing), which are not discussed in this article. The full report[9] provides additional details on the methods, results, and contextual issues addressed.

Data Sources and Searches

Ovid MEDLINE, PubMed (publisher-supplied records only), and the Cochrane Central Register of Controlled Trials were searched to locate primary studies informing the key questions (eMethods in the Supplement). Searches included literature published between January 1, 2015, and December 4, 2019. The searches were supplemented with expert suggestions and by reviewing reference lists from other relevant systematic reviews, including the 2016 USPSTF evidence report.[4] Ongoing surveillance was conducted through March 26, 2021, through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence. Two new studies were identified[10,11]; however, they did not substantively change the review's interpretation of findings or conclusions and are not discussed further.

Study Selection

Two independent reviewers screened the titles, abstracts, and relevant full-text articles to ensure consistency with a priori inclusion and exclusion criteria (eTable 1 in the Supplement). Included studies were English-language studies of asymptomatic screening populations of individuals 40 years or older who were either at average risk for CRC or not selected for inclusion based on CRC risk factors. Studies that evaluated direct visualization (ie, colonoscopy, flexible sigmoidoscopy, computed tomography [CT] colonography) or currently available stool-based (ie, guaiac fecal occult blood test [gFOBT], fecal immunochemical test [FIT], stool DNA with a FIT [sDNA-FIT]), or serum-based (ie, methylated *SEPT9* gene) tests were included.

For KQ1, randomized clinical trials (RCTs) or nonrandomized controlled intervention studies of CRC screening vs no screening or trials comparing screening tests were included. Included studies needed to report outcomes of CRC incidence, CRC-specific mortality, or all-cause mortality. For tests without trial-level evidence, well-conducted prospective cohort studies were included.

For KQ2, test accuracy studies that used colonoscopy as the reference standard were included. Well-conducted test accuracy studies that used robust registry follow-up for screen-negative participants were also included. Studies whose design was subject to a high risk of bias were excluded, including those studies subject to verification bias, spectrum bias, or both.[12-16]

For KQ3, all trials and observational studies that reported serious adverse events requiring unexpected or unwanted medical attention or resulting in death were included. These events included, but were not limited to, perforation, major bleeding, severe abdominal symptoms, and cardiovascular events. Studies designed to assess for extracolonic findings (ie, incidental findings on CT colonography) and the resultant diagnostic yield and harms of workup were also included.

Data Extraction and Quality Assessment

Two reviewers critically appraised all articles that met inclusion criteria using prespecified quality criteria (eTable 2 in the Supplement).[8] Disagreements about critical appraisal were resolved by consensus. Poor-quality studies (ie, those with methodological shortcomings resulting in a high risk of bias) were excluded. One reviewer extracted descriptive information and outcome data into standardized evidence tables and a second reviewer checked the data for accuracy.

Data Synthesis and Analysis

The results were synthesized by KQ, type of screening test, and study design. For KQ1, the syntheses were organized into 3 main categories: (1) trials designed to assess the effectiveness (intention to screen) of screening tests compared with no screening; (2) observational studies designed to assess the association of receipt of a screening test compared with no screening; and (3) comparative trials of one screening test vs another screening test. Many of the trials comparing screening tests that met inclusion criteria, however, were designed to determine the differential uptake of tests, determine the comparative yield between tests, or both. As such, they were not powered to detect differences in CRC outcomes or mortality (ie, comparative effectiveness) and are not discussed in this article. When data were available, random-effects meta-analyses were conducted using the restricted maximum likelihood method to estimate the pooled incidence rate ratio (IRR).

For KQ2, the analyses primarily focused on per-person test accuracy of a single test application to detect CRC, advanced adenomas, advanced neoplasia, and adenomas by size (≥6 mm or ≥10 mm). When possible, data from contingency tables was analyzed using a bivariate model, which modeled sensitivity and specificity simultaneously. Although studies evaluating stool-based tests using

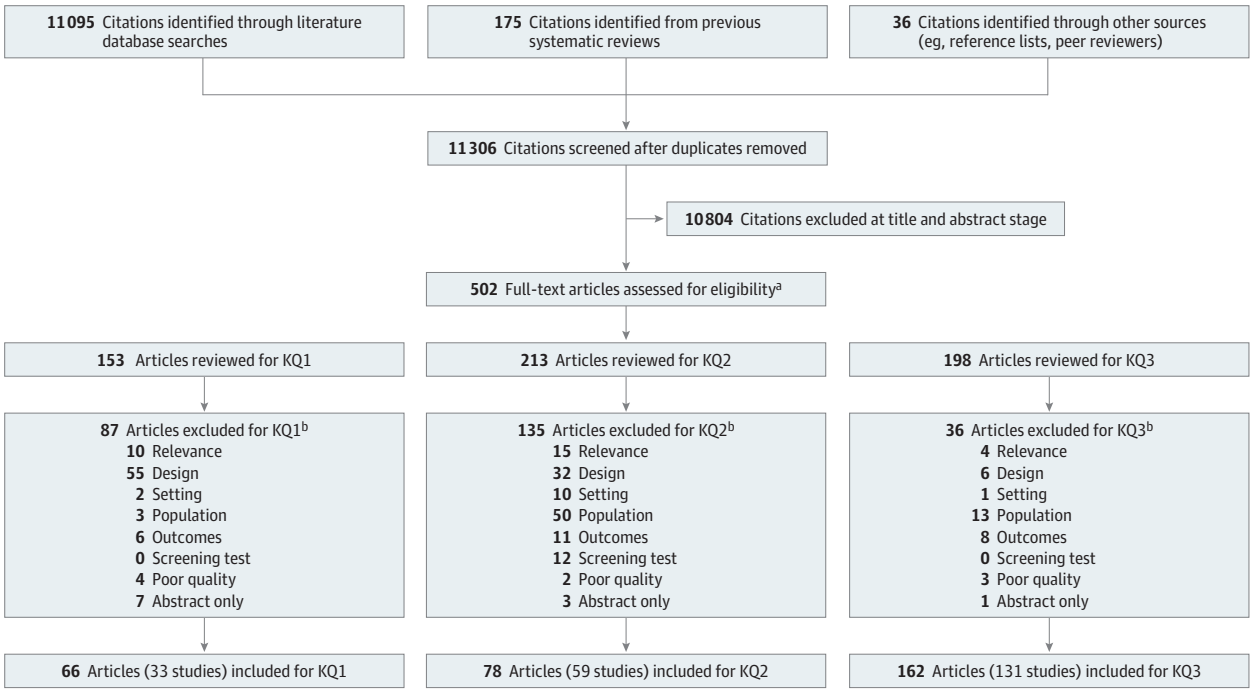
Figure 1. Analytic Framework: Screening for Colorectal Cancer

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Additional information available in the USPSTF Procedure Manual.[8] FIT indicates fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; m*SEPT9*, methylated septin 9 gene; sDNA test, stool DNA test; SSP, sessile serrated polyp.

[a] Screening technology with conditional approval from the US Food and Drug Administration for screening for colorectal cancer.

[b] Screening modality not discussed in this article.

Figure 2. Literature Search Flow Diagram: Screening for Colorectal Cancer



KQ indicates key question.

[a] Articles could be reviewed for more than 1 KQ.

[b] Reasons for exclusion: Relevance: Study aim not relevant. Design: Study did not use an included design. Setting: Study not conducted in a country relevant to US practice or not conducted in, recruited from, or feasible for primary care or a health system. Population: Study not conducted in an included population. Outcomes: Study did not have relevant outcomes or had incomplete outcomes. Screening test: Screening test was out of scope. Quality: Study was poor quality. Abstract only: Full-text publication not available.

a colonoscopy reference standard for all persons and studies using a registry follow-up for screen-negative persons were included, only results from the former study design are detailed in this article. For the FITs, random-effects meta-analyses were conducted by test "family" (ie, tests produced by the same manufacturer, using the same components and method and compatible automated analyzers) and by cutoff values (in μg Hb/g feces).

For KQ3, there were no hypothesized serious harms for stool-, blood-, or serum-based tests beyond test inaccuracy and harms accrued from subsequent colonoscopy. Harms for direct visualization tests were categorized by indication (ie, screening vs follow-up for an abnormal flexible sigmoidoscopy or stool test). For colonoscopy and flexible sigmoidoscopy, random-effects meta-analyses using the DerSimonian and Laird method were conducted to estimate rates of perforation and major bleeding.

All quantitative analyses were conducted in Stata version 16 (StataCorp). The presence of statistical heterogeneity was assessed among pooled studies using the I^2 statistic. All tests were 2-sided, with $P < .05$ indicating statistical significance.

The aggregate strength of evidence (ie, high, moderate, or low) was subsequently assessed for each KQ using the approach described in the Methods Guide for the Effectiveness and Comparative Effectiveness Reviews,[17] based on consistency, precision, reporting bias, and study quality.

Results

Investigators reviewed 11 306 unique citations and 502 full-text articles for all KQs (**Figure 2**). Overall, 196 studies reported in 255 publications were included, 70 of which were newly identified since the prior review. A full list of included studies by KQ is available in the Supplement.

Benefits of Screening

Key Question 1. What is the effectiveness or comparative effectiveness of screening in reducing colorectal cancer, mortality, or both?

Thirty-three unique fair- to good-quality studies (n = 10 776 276)[18-50] (published in 66 articles[18-83]) were included to assess the effectiveness or comparative effectiveness of screening tests on CRC incidence and mortality. These included 2 prospective cohort studies[37,47] (n = 436 927) that examined the effectiveness of screening colonoscopy, 4 RCTs[19,24,29,35] (n = 458 002) that examined the effectiveness of flexible sigmoidoscopy with or without a FIT, 6 trials[20,21,27,36,38,39] (n = 525 966) that examined the effectiveness of a gFOBT, and 1 prospective cohort study[46] (n = 5 417 699) that examined the effectiveness of a FIT. In addition to 1 screening RCT[19] (n = 98 678) that evaluated flexible sigmoidoscopy plus FIT vs flexible sigmoidoscopy alone, 20

Table 1. Key Question 1: Overall Summary of Impact of Screening vs No Screening on Colorectal Cancer Incidence and Mortality

Screening test (sample No.)	No. of studies (participants)	Rounds (intervals)	Follow-up, y	CRC incidence	CRC mortality
Colonoscopy[37,47]	2 cohort studies[a] (n = 436 927)	1	8-24[b]	With polypectomy: HR, 0.53 (95% CI, 0.40 to 0.71)[c] Negative colonoscopy result: HR, 0.47 (95% CI, 0.39 to 0.57)[c] Age 70-74 y: RD, −0.42% (95% CI, −0.24% to −0.63%)[d] Age 75-79 y: RD, −0.14% (95% CI, −0.41% to −0.16%)[d]	HR, 0.32 (95% CI, 0.24 to 0.45)[c]
Flexible sigmoidoscopy[19,24,29,35]	4 RCTs[a] (n = 458 002)	1-2 (every 3-5 y)	11-17	IRR, 0.78 (95% CI, 0.74 to 0.83)	IRR, 0.74 (95% CI, 0.68 to 0.80)
Hemoccult II[20,21,27,36,39]	5 RCTs[e] (n = 419 966)	2-9 (every 2 y)	11-30	RR range, 0.90 (95% CI, 0.77 to 1.04) to 1.02 (95% CI, 0.93 to 1.12)	RR range, 0.78 (95% CI, 0.65 to 0.93) to 0.91 (95% CI, 0.84 to 0.98)[f]
FIT[46]	1 cohort study[a] (n = 5.4 million)	Every 2 y	6 (mean, 3)	NR	RR, 0.90 (95% CI, 0.84 to 0.95)

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; HR, hazard ratio; IRR, incidence rate ratio; NR, not reported; RCT, randomized clinical trial; RD, risk difference; RR, relative risk.

[a] Includes newly identified studies or newly identified articles with additional follow-up to a previously included study.

[b] Twenty-two–year follow-up for incidence; 24-year follow-up for mortality.

[c] Adjusted for age, body mass index, family history, smoking status, physical activity, diet, vitamin use, aspirin use, nonsteroidal anti-inflammatory drug use, cholesterol-lowering drug use, hormone replacement therapy.

[d] Standardized 8-year risk.

[e] One RCT in Finland that only has interim follow-up is not represented in this table (n = 360 492).

[f] Annual RR from 1 trial only, 0.68 (95% CI, 0.56-0.82); 11 rounds every 1 year, 30-year follow-up.

studies[18,22,23,25,26,28,30-34,40-45,48-50] (n = 471 860) that compared screening modalities were included. The magnitude of benefit in CRC mortality and cancer incidence among screening tests could not be directly compared because of major differences in the design of included studies for each test type (eg, trial vs observational study, intention to screen vs as screened, outcome metric reported). No studies were found evaluating the effectiveness of CT colonography, high-sensitivity gFOBT, sDNA with or without FIT, or serum tests on CRC incidence, CRC mortality, or both.

Colonoscopy

Two large, prospective observational studies[37,47] (n = 436 927) evaluating the association of receipt of screening colonoscopy with CRC incidence or mortality were included (**Table 1**). After 24 years of follow-up, 1 study among health professionals (n = 88 902) found that the CRC-specific mortality rate was lower in people who self-reported at least 1 screening colonoscopy compared with those who had never had a screening colonoscopy (adjusted hazard ratio, 0.32 [95% CI, 0.24-0.45]).[37] This study found that screening colonoscopies were associated with lower CRC mortality from both distal and proximal cancers. Another study conducted among Medicare beneficiaries (n = 348 025) with much shorter follow-up found that people aged 70 to 74 years who underwent a screening colonoscopy had a lower 8-year standardized risk for CRC (−0.42% [95% CI, −0.24% to −0.63%]) than those who did not undergo the test.[47]

Flexible Sigmoidoscopy

Four well-conducted trials[19,24,29,35] (n = 458 002) of 1- or 2-time flexible sigmoidoscopy screening that demonstrated a reduction in CRC incidence and mortality were included (Table 1). All 4 trials were included in the previous review. While 3 of these trials have published longer follow-up since the previous review,[19,24,29] the new data did not change the conclusions on screening effectiveness. Based on 4 RCTs that used intention-to-screen analyses, 1- or 2-time flexible sigmoidoscopy was consistently associated with a decrease in CRC incidence (IRR, 0.78 [95% CI, 0.74-0.83], with 28 to 47 fewer CRC cases per 100 000 person-years) and CRC-specific mortality (IRR, 0.74 [95% CI, 0.68-0.80], with 10 to 17 fewer CRC deaths per 100 000 person-years) when compared with no screening at 11 to 17 years of follow-up (eFigure 1 in the Supplement).

Guaiac Fecal Occult Blood Test

Six well-conducted trials[20,21,27,36,38,39] (n = 780 458) of biennial or annual gFOBT screening that demonstrated a reduction in CRC incidence and mortality were included (Table 1). Based on 5 RCTs[20,21,27,36,39] (n = 419 966) that used intention-to-screen analyses, biennial screening with Hemoccult II (Beckman Coulter) was associated with a reduction of CRC-specific mortality compared with no screening after 2 to 9 rounds of screening at 11 to 30 years of follow-up (relative risk [RR], 0.91 [95% CI, 0.84-0.98] at 19.5 years; RR, 0.78 [95% CI, 0.65-0.93] at 30 years) (eTable 3 in the Supplement). One additional trial[38] of screening with Hemoccult II in Finland (n = 360 492) reported only interim findings, with a follow-up of 4.5 years.

Fecal Immunochemical Test

Although many observational studies have evaluated national FIT screening programs, only 1 prospective observational study[46] (n = 5 417 699) that evaluated receipt of FIT on CRC incidence, CRC mortality, or both met the inclusion criteria (Table 1). This study found that 1 to 3 rounds of screening with a biennial FIT (OC-Sensor [Eiken Chemical] or HM JACK [Kyowa Medex]) were associated with lower CRC mortality at 6 years' follow-up, compared with no screening (adjusted RR, 0.90 [95% CI, 0.84-0.95]).[46]

Comparative Effectiveness

In 1 flexible sigmoidoscopy screening RCT (n = 98 678), compared with persons in the no screening group, persons in the flexible sigmoidoscopy plus FIT group had lower risk of CRC-specific mortality than those in the flexible sigmoidoscopy–only group (age-adjusted

Table 2. Key Question 2: Summary of Test Accuracy Results for Direct Visualization Screening Tests[a]

Screening test group	No. of studies	No. of participants	CRC Sensitivity (95% CI)	Adenomas ≥10 mm Sensitivity (95% CI)	Adenomas ≥10 mm Specificity (95% CI)	Adenomas ≥6 mm Sensitivity (95% CI)	Adenomas ≥6 mm Specificity (95% CI)
Flexible sigmoidoscopy	0	NA	NA	NA	NA	NA	NA
CT colonography[b]	7	5328	0.86-1.0 (0.21-1.0)	0.89 (0.83-0.96)	0.94 (0.89-1.0)	0.86 (0.78-0.95)	0.88 (0.83-0.95)
Colonoscopy	4	4821	0.18-1.0 (0.01-1.0)	0.89-0.95 (0.70-0.99)	0.89 (0.86-0.91)[c]	0.75-0.93 (0.63-0.96)	0.94 (0.92-0.96)[c]

Abbreviations: CRC, colorectal cancer; CT, computed tomography; NA, not available.

[a] Pooled estimates from meta-analysis when available; otherwise, range of values and range of the 95% CI reported.

[b] Test accuracy shown for CT colonography with bowel preparation only. Two additional studies without bowel preparation are not represented in this table.

[c] Only 1 study reported specificity.

hazard ratio, 0.62 [95% CI, 0.42-0.90] vs 0.84 [95% CI, 0.61-1.17]), although this difference was not statistically significant.[19] Additional included trials were primarily designed to evaluate the comparative uptake/adherence, test positivity, and initial cancer detection of one screening test vs another. Several adequately powered studies currently underway are evaluating the comparative effectiveness of direct visualization vs stool-based screening programs (eTable 4 in the Supplement).

Findings by Age, Sex, and Race/Ethnicity

Overall, age stratified analyses from flexible sigmoidoscopy and gFOBT trials did not demonstrate statistically significant differences in benefit in older vs younger adults, although age strata used were not consistent across trials. Only 3 gFOBT studies included adults younger than 50 years at recruitment, and none of these studies provided age-stratified analyses for this age group.[27,36,39] One study evaluating receipt of screening colonoscopy among Medicare beneficiaries did not find a benefit in 8-year standardized risk for CRC in those aged 75 to 79 years, in contrast to the benefit seen in those aged 70 to 74 years.[47] Reductions in CRC incidence (eFigure 2 in the Supplement) and mortality (eFigure 3 in the Supplement) from flexible sigmoidoscopy trials were greater for men than for women. This evidence, however, was less consistent in 3 trials that reported sex differences for gFOBT screening programs.

Accuracy of Screening

Key Question 2. What is the accuracy of direct visualization, stool-based, or serum-based screening tests for detecting colorectal cancer, advanced adenomas, or adenomatous polyps based on size?

Fifty-nine studies[84-142] (n = 3 491 045) (published in 78 articles[84-161]) that evaluated the accuracy of various screening tests were included. There were no new studies published since the prior review that would add to the understanding of screening sensitivity or specificity for colonoscopy, CT colonography, or flexible sigmoidoscopy. New studies were identified that evaluated the sensitivity and specificity of stool-based (ie, high-sensitivity gFOBT, FIT, sDNA-FIT) and serum-based tests for screening.

Colonoscopy and CT Colonography

Nine fair- to good-quality studies[102,105,110,111,114,117,121,128,138] (n = 6497) that evaluated screening CT colonography were included, 4 of which (n = 4821) also reported the test accuracy of colonoscopy (**Table 2**).[110,111,128,138] Based on these studies, while both colonoscopy and CT colonography did not accurately identify all cancers, the number of CRCs in these studies was low and these studies were not powered to estimate the test accuracy for CRC.

Based on 3 studies[111,128,138] (n = 2290) that compared colonoscopy to a reference standard of CT colonography–enhanced colonoscopy or repeat colonoscopy, the per-person sensitivity for adenomas 10 mm or larger ranged from 0.89 (95% CI, 0.78-0.96) to 0.95 (95% CI, 0.74-0.99). The per-person sensitivity for adenomas 6 mm or larger ranged from 0.75 (95% CI, 0.63-0.84) to 0.93 (95% CI, 0.88-0.96). Specificity could be calculated only from 1 of the included studies and was 0.89 (95% CI, 0.86-0.91) for adenomas 10 mm or larger and 0.94 (95% CI, 0.92-0.96) for adenomas 6 mm or larger.[138]

Based on 7 studies[105,110,111,114,117,121,128] (n = 5328) evaluating CT colonography with bowel preparation, the sensitivity to detect adenomas 10 mm or larger ranged from 0.67 (95% CI, 0.45-0.84) to 0.94 (95% CI, 0.84-0.98) and specificity ranged from 0.86 (95% CI, 0.85-0.87) to 0.98 (95% CI, 0.96-0.99) (eFigure 4 in the Supplement). Likewise, the sensitivity to detect adenomas 6 mm or larger ranged from 0.73 (95% CI, 0.58-0.84) to 0.98 (95% CI, 0.91-0.99) and specificity ranged from 0.80 (95% CI, 0.77-0.82) to 0.93 (95% CI, 0.90-0.96) (eFigure 5 in the Supplement). Although there was some variation in estimates of sensitivity and specificity among included studies, it remains unclear whether the variation of test performance was due to differences in study design, populations, CT colonography imaging, reader experience, or reading of protocols.

High-Sensitivity gFOBT

Two[84,133] (n = 3503) of the 5 studies that evaluated Hemoccult Sensa (Beckman Coulter) applied a colonoscopy reference standard to all persons (**Table 3**). In these 2 studies, the sensitivity to detect CRC ranged from 0.50 to 0.75 (95% CI range, 0.09-1.0) and specificity ranged from 0.96 to 0.98 (95% CI range, 0.95-0.99). Hemoccult Sensa was not sensitive to detect advanced adenocarcinoma (sensitivity range, 0.06-0.17; 95% CI range, 0.02-0.23).

Fecal Immunochemical Test

There are a wide variety of FITs available. Those most commonly evaluated in this review were part of the OC-Sensor family (Eiken Chemical; includes tests OC FIT-CHEK, OC-Auto, OC-Micro, OC-Sensor, and OC-Sensor Micro) or the OC-Light test (by the same manufacturer but using a different methodology) (Table 3). Based on 9 studies[89,97,100,107,108,113,127,130,133] (n = 34 352) that used OC-Sensor tests to detect CRC with a colonoscopy reference standard

Table 3. Key Question 2: Summary of Test Accuracy Results From Studies With Colonoscopy Follow-up for Stool and Serum Screening Tests[a]

Screening test group	No. of studies	No. of participants	CRC		Advanced neoplasia		Advanced adenoma	
			Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
High-sensitivity gFOBT: Hemoccult Sensa	2[b]	3503	0.50-0.75 (0.09-1.0)	0.96-0.98 (0.95-0.99)	0.07-0.21 (0.02-0.27)	0.96-0.99 (0.96-0.99)	0.06-0.17 (0.02-0.23)	0.96-0.99 (0.96-0.99)
FIT								
OC-Sensor	13[b,c]	44 887	0.74 (0.64-0.83)	0.94 (0.93-0.96)	0.25 (0.21-0.31)	0.96 (0.95-0.97)	0.23 (0.20-0.25)	0.96 (0.95-0.97)
OC-Light	4[b]	32 424	0.81 (0.70-0.91)	0.93 (0.91-0.96)	0.27 (0.16-0.38)	0.95 (0.92-0.98)	0.28 (0.19-0.37)	0.94 (0.91-0.97)
Other	12[b,c]	53 527	0.50-0.97 (0.09-1.00)	0.83-0.97 (0.82-0.97)	0.02-0.66 (0.01-0.99)	0.60-0.99 (0.58-1.0)	0.18-0.50 (0.13-0.56)	0.85-0.98 (0.84-0.98)
mtsDNA-FIT: Cologuard	4[b]	12 424	0.93 (0.87-1.0)	0.85 (0.84-0.86)	0.47 (0.44-0.50)	0.89 (0.87-0.92)	0.43 (0.40-0.46)	0.89 (0.86-0.92)
Serum: Epi proColon	1	6857	0.68 (0.53-0.80)	0.79 (0.77-0.81)	0.25 (0.22-0.28)	0.79 (0.76-0.82)	0.22 (0.18-0.24)	0.79 (0.76-0.82)

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; mtsDNA, multitargeted stool-based DNA.

[a] Pooled estimates and 95% CI from meta-analysis when available; otherwise, range of values and range of the 95% CIs reported.

[b] Includes newly identified studies.

[c] One nested case-control study[104] (n = 516) is not represented in this table.

and the manufacturer-recommended cutoff of 20 µg Hb/g feces, pooled sensitivity was 0.74 (95% CI, 0.64 to 0.83; I^2 = 31.6%) and pooled specificity was 0.94 (95% CI, 0.93-0.96; I^2 = 96.6%) (eFigure 6 in the Supplement). As expected at lower cutoffs (10 and 15 µg Hb/g feces), the sensitivity increased and the corresponding specificities decreased. Based on 10 studies[89,91,97,100,107,108,113,127,130,133] (n = 40 411) that used OC-Sensor tests to detect advanced adenocarcinoma with a colonoscopy reference standard, sensitivity using a cutoff of 20 µg Hb/g feces was 0.23 (95% CI, 0.20-0.25; I^2 = 47.4%) and specificity was 0.96 (95% CI, 0.95-0.97; I^2 = 94.8) (eFigure 7 in the Supplement). Based on 3 studies[95,96,98] (n = 31 803), OC-Light had similar sensitivity and specificity to detect CRC and advanced adenocarcinoma compared with OC-Sensor.

sDNA (With or Without FIT)

The only available sDNA screening test includes a FIT assay marketed as Cologuard (Exact Sciences), which is sometimes referred to as a multitarget stool DNA test. Based on 4 studies[99,108,130,142] (n = 12 424) to detect CRC using a colonoscopy, pooled sensitivity was 0.93 (95% CI, 0.87-1.0) and pooled specificity was 0.85 (95% CI, 0.84-0.86); to detect advanced adenoma, pooled sensitivity was 0.43 (95% CI, 0.40-0.46) and pooled specificity was 0.89 (95% CI, 0.86-0.92) (Table 3; eFigure 8 in the Supplement).

Serum Test

Currently, one serum test—Epi proColon (Epigenomics)—is available to screen average-risk adults for CRC through detection of circulating methylated *SEPT9* DNA. Based on 1 fair-quality nested case-control study[129] (n = 6857), sensitivity to detect CRC was 0.68 (95% CI, 0.53-0.80) and specificity was 0.79 (95% CI, 0.77-0.81) (Table 3). The sensitivity to detect advanced adenoma was 0.22 (95% CI, 0.18-0.24) and specificity was 0.79 (95% CI, 0.76-0.82).

Findings by Age, Sex, and Race/Ethnicity

While FIT studies that examined differences in test accuracy by age, sex, or race/ethnicity were limited, no consistent differences by subgroup were found. Overall, in 10 studies there were no significant differences in test accuracy by age strata, including 2 studies reporting stratified analyses for persons younger than 50 years; however, 2 studies suggested possible lower specificity to detect CRC in older persons (70 years or older). Six studies reported test accuracy by sex and produced inconsistent findings. One OC-Sensor study reported no difference in test accuracy for advanced neoplasia in Black vs White participants.[99]

The largest study[108,162] on sDNA-FIT reported test accuracy by age, sex, and race/ethnicity groups, although this study was not designed to examine these differences. This study found that the specificity to detect CRC and advanced adenoma decreases as age increases, but there was not a clear pattern for increasing sensitivity with increasing age. Findings were inconsistent in 2 studies that reported test accuracy for White participants compared with Black participants.

Harms of Screening

Key Question 3. What are the serious harms of the different screening tests?

One hundred thirty-one fair- or good-quality studies[18-29,33-36,43,47,49,102,105,110,114,117,128,131,138,163-266] (published in 162 articles[18-29,33-36,43,47,49,51-54,56-58,60,61,64,65,68,69,71-80,102,105,110,114,117,128,131,138,143,163-273]) were included. Among these, 18 studies[19,22,24,28,29,33-35,49,203,206,212,216,234,235,239,254,260] (n = 395 077) evaluated serious harms from screening flexible sigmoidoscopy; 67 studies[26,43,47,163,164,166,168,171,172,174,179,180,182-189,191-195,197-199,201,203-205,210,213,215-218,226,229,231,233,237-252,255,256,258,261-266] (n = 25 784 107) evaluated screening colonoscopy; 21 studies[19-21,24,26,27,29,34-36,49,169,172,173,175-177,181,225,227,236] (n = 903 872) evaluated colonoscopy following an abnormal result from a stool test, flexible sigmoidoscopy, or CT colonography; and 38 studies[18,23,43,102,105,110,114,117,128,138,165,167,170,178,189,190,196,200,202,203,207-211,214,219-224,228,230,232,253,257,259] (n = 140 607) evaluated CT colonography. Of the studies evaluating CT colonography, 7 studies[102,105,117,138,202,203,253] (n = 3365) provided estimates of radiation exposure and 27 studies[18,23,43,110,128,138,165,167,170,178,200,207-211,214,219-224,230,232,257,259] (n = 48 235) reported extracolonic findings. While no studies examined the harms of stool or serum testing, there are not hypothesized serious harms for these noninvasive tests

Table 4. Key Question 3: Summary of Serious Harms and Extracolonic Findings From Screening

Modality	Outcome	No. of studies	No. of participants	Events per 10 000 procedures (95% CI)
Screening flexible sigmoidoscopy	Serious bleeding	10	179 854	0.50 (0.0-1.30)
	Perforation	11	359 679	0.20 (0.10-0.40)
Screening colonoscopy	Serious bleeding	20	5 172 508	14.6 (9.4-19.9)
	Perforation	26	5 272 600	3.1 (2.3-4.0)
Colonoscopy following abnormal stool test result	Serious bleeding	11	78 793	17.5 (7.6-27.5)
	Perforation	12	341 922	5.4 (3.4-7.4)
Colonoscopy following abnormal flexible sigmoidoscopy result	Serious bleeding	4	5790	20.7 (8.2 to 33.2)
	Perforation	4	23 022	12.0 (7.5 to 16.5)
CT colonography	Radiation exposure	7	NA	≈1 to 5 mSv per examination
	ECF	27	48 235	E4: 3.4%-26.9% of CT colonography examinations; E3: 1.3%-11.4% of CT colonography examinations[a]

Abbreviations: CT, computed tomography; ECF, extracolonic finding; NA, not available.

[a] Based on CT Colonography Reporting and Data System categorization of ECFs, where E3 = likely unimportant or incompletely characterized finding for which workup may be required and E4 = potentially important finding requiring follow-up.[274]

other than diagnostic inaccuracy (ie, false-positive or false-negative test results) or downstream harms of follow-up tests.

Serious adverse events from colonoscopy among screening populations were estimated at 3.1 perforations (95% CI, 2.3-4.0) per 10 000 procedures (26 studies, n = 5 272 600) and 14.6 major bleeding events (95% CI, 9.4-19.9) per 10 000 procedures (20 studies, n = 5 172 508) (**Table 4**). Serious adverse events from screening flexible sigmoidoscopy alone were less common, with a pooled estimate of 0.2 perforations (95% CI, 0.1-0.4) per 10 000 procedures (11 studies, n = 359 679) and 0.5 major bleeding events (95% CI, 0-1.3) per 10 000 procedures (10 studies, n = 179 854). However, for colonoscopies following flexible sigmoidoscopy with abnormal findings, the pooled estimates were 12.0 perforations (95% CI, 7.5-16.5) per 10 000 colonoscopy procedures (4 studies, n = 23 022) and 20.7 major bleeding events (95% CI, 8.2-33.2) per 10 000 colonoscopy procedures (4 studies, n = 5790). Serious adverse events from colonoscopy following stool testing with an abnormal result were estimated at 5.4 perforations (95% CI 3.4-7.4) per 10 000 colonoscopy procedures (12 studies, n = 341 922) and 17.5 serious bleeding events (95% CI, 7.6-27.5) per 10 000 colonoscopy procedures (11 studies, n = 78 793). Other harms which may result from screening, such as cardiopulmonary events or infections, are best assessed using comparative study designs. Only 4 studies[47,187,191,262] (n = 4 173 949) reported harms in a cohort that received colonoscopy compared with a cohort that did not. These studies did not find a higher risk of serious harms associated with colonoscopy.

Data from 17 studies (n = 89 073) showed little to no risk of serious adverse events (eg, symptomatic perforation) for screening CT colonography. While CT colonography may also require a follow-up colonoscopy, sufficient evidence was not found to estimate serious adverse events from colonoscopy follow-up. CT colonography also entails exposure to low-dose ionizing radiation (range, 0.8 to 5.3 mSv), which may increase the risk of malignancy. Additionally, extracolonic findings on CT colonography were common (eTable 5 in the Supplement) (27 studies, n = 48 234). Approximately 1.3% to 11.4% of CT colonographies had potentially important extracolonic findings (CT Colonography Reporting and Data System [C-RADS] category E4) that necessitated diagnostic follow-up. Additionally, 3.4% to 26.9% of CT colonographies had C-RADS category E3 findings, some of which may require additional workup because of incompletely characterized findings. Although some included studies did report the final diagnosis of extracolonic findings, it is still unclear if the detection of extracolonic findings represents an overall benefit (detection and treatment of clinically significant disease) or harm (unnecessary diagnostic workup or identification of condition not needing intervention).

Findings by Age, Sex, and Race/Ethnicity

Twenty-three studies provided analyses of differential harms of colonoscopy by age. These studies generally found increasing rates of serious adverse events with increasing age, including perforation and bleeding. Sex differences in serious harms, when reported in 12 studies, suggested little differential risk between men and women. There were inconsistent findings in 4 studies that report harm stratified by race/ethnicity.

In 4 studies, extracolonic findings on CT colonography were more common with increasing age.[110,208,209,211] Three studies reported extracolonic findings by sex, finding similar rates of extracolonic findings in both groups.[207,219,221]

Discussion

This systematic review assessed the effectiveness, test accuracy, and harms of CRC screening. A summary of the identified evidence is shown in **Table 5**. Since the 2016 USPSTF recommendation, more evidence has been published on the effectiveness and test accuracy of newer stool tests (FIT and sDNA-FIT) and the test accuracy of a US Food and Drug Administration–approved serum test (Epi proColon) for use in persons declining colonoscopy, flexible sigmoidoscopy, gFOBT, or FIT. More data on colonoscopy harms have also been published that reported higher estimates of major bleeding than previously appreciated. Overall, the different screening tests evaluated have different levels of evidence to demonstrate their ability to reduce cancer mortality and to detect cancer, precursor lesions, or both as well as their risk of serious adverse events.

Table 5. Summary of Evidence

Instrument or treatment	Study design (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: Benefits of screening						
Flexible sigmoidoscopy	4 RCTs (n = 458 002)	One- or 2-time flexible sigmoidoscopy decreased CRC mortality compared with no screening at 11-17-y follow-up (IRR, 0.74 [95% CI, 0.68-0.80])	Consistent, precise	Only PLCO evaluated more than 1 round of screening Variation in referral criteria led to differing rates of follow-up colonoscopy	High	No longer widely used in the US No studies included people younger than 50 y
Colonoscopy	2 Cohort studies (n = 436 927)	One study found CRC mortality was lower in people with at least 1 screening colonoscopy vs those who never had a screening colonoscopy after 24-y follow-up (adjusted HR, 0.32 [95% CI, 0.24-0.45]) Another study in people aged 70-74 y found CRC incidence was lower in people who had a screening colonoscopy vs those who did not after 8 y (standardized risk, 0.42% [95% CI, 0.24%-0.63%])	Consistent, imprecise	Variation in underlying risk for CRC, length of follow-up, and outcomes reported (only 1 study reported CRC mortality)	Low	Studies limited to health professionals and older adults Based on subgroup analyses, findings not applicable to people with first-degree relatives with CRC or to adults aged 75-79 y One study included people younger than 50 y
gFOBT	6 RCTs (n = 780 458)	Biennial screening with Hemoccult II decreased CRC-specific mortality compared with no screening after 2-9 rounds of screening at 11-30 y of follow-up (RR range, 0.91 [95% CI, 0.84-0.98] at 19.5 y to 0.78 [95% CI, 0.65-0.93] at 30 y) One trial in Finland (n = 360 492) reported only interim findings, with a follow-up of 4.5 y	Consistent, precise	Variation in number of screening rounds, use of rehydrated samples, definition of test positive, and recommended follow-up	High	Hemoccult II no longer widely used in US Three trials included people younger than 50 y
FIT	1 Cohort study (n = 5 417 699)	One to 3 rounds of biennial FIT were associated with lower CRC mortality compared with no screening at up to 6 y follow-up (adjusted RR, 0.90 [95% CI, 0.84-0.95])	NA	Limited follow-up (mean, 3 y)	Low	Study conducted in Taiwan FITs used include OC-Sensor and HM JACK Did not include participants younger than 50 y
Comparative effectiveness	20 RCTs (n = 386 711) 1 Cohort study (n = 85 149)	Trials comparing different screening tests do not provide evidence of comparative benefit on CRC incidence or mortality outcomes[a] Limited data suggest that 4 rounds of FIT detects a similar number of cancers as 1-time colonoscopy or flexible sigmoidoscopy; FIT can detect more cancers than Hemoccult II; 2-sample FIT does not appear superior to 1-sample FIT; and no statistically significant differences in cancer detection after 1-2 rounds of testing between FITs, despite differences in test positivity	Inconsistent, imprecise	Few trials powered to detect effect of screening on mortality; limited to a single round of screening Overall low number of cancers detected, and few interval cancers reported	Insufficient	No studies evaluating comparative effectiveness of capsule endoscopy, sDNA, serum, or urine tests No studies included people younger than 50 y

(continued)

Table 5. Summary of Evidence (continued)

Instrument or treatment	Study design (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ2: Accuracy of screening						
Colonoscopy	4 Studies, colonoscopy + CT colonography reference standard (n = 4821)	CRC: Sensitivity range, 0.18 to 1.0 (95% CI range, 0.01 to 1.0) Adenoma ≥10 mm: Sensitivity range, 0.89 to 0.95 (95% CI range, 0.74 to 1.0); specificity, 0.89 (95% CI, 0.86-0.91) Adenoma ≥6 mm: Sensitivity range, 0.75 to 0.93 (95% CI range, 0.63 to 0.96); specificity, 0.94 (95% CI, 0.92-0.96)	Consistent, imprecise	Studies not designed to assess test accuracy to detect cancers Specificity could only be calculated from 1 study	Moderate	Colonoscopies were conducted or supervised by "experienced" specialists Two studies included people younger than 50 y (1 only if they had a family history)
CT colonography	9 Studies, colonoscopy + CT colonography reference standard (n = 6497)	CRC:[b] Sensitivity range, 0.86 to 1.0 (95% CI range, 0.21 to 1.0) Adenoma ≥10 mm:[b] Sensitivity, 0.89 (95% CI, 0.83-0.96; I^2 = 41.7%); specificity, 0.94 (95% CI, 0.89-1.0; I^2 = 98.3%) Adenoma ≥6 mm:[b] Sensitivity, 0.86 (95% CI, 0.78-0.95; I^2 = 87.4%); specificity, 0.88 (95% CI, 0.83-0.95; I^2 = 94.9%)	CRC: consistent, imprecise Adenomas: consistent, precise	Studies not designed to assess test accuracy to detect cancers Unclear if variation in test performance is attributable to differences in study design, population, CT colonography imaging, or reader experience or reading protocols	Moderate	Estimates apply to CT colonography with full bowel prep Mostly single-center studies using limited number of highly trained radiologists; current practice may use lower doses of radiation (and therefore different technology/protocols) Four studies included people younger than 50 y (2 only if they had a family history)
High-sensitivity gFOBT	2 Studies, colonoscopy reference standard (n = 3503) 3 Studies, registry reference standard (n = 15 969)	CRC: Sensitivity range, 0.50 to 0.75 (95% CI range, 0.09 to 1.0); specificity range, 0.96 to 0.98 (95% CI range, (0.95 to 0.99) Advanced adenoma: sensitivity range, 0.06 to 0.17 (95% CI range, 0.02 to 0.23); specificity range, 0.96 to 0.99 (95% CI range, 0.96 to 0.99) Estimates for sensitivity to detect CRC were slightly higher in studies using differential reference standard (registry follow-up)	Inconsistent, imprecise	Only 2 studies without verification bias, with varying estimates	Low	Estimates apply to Hemoccult SENSA; test is no longer widely used in the US and requires 3 stool samples and dietary restrictions Did not include people younger than 50 y
FIT	25 Studies, colonoscopy reference standard (n = 122 370) 18 Studies, registry reference standard (n = 2 824 358)	CRC:[c] Sensitivity, 0.74 (95% CI, 0.64-0.83); I^2 = 31.6%; specificity, 0.94 (95% CI, 0.93-0.96); I^2 = 96.6% Advanced adenoma:[c] Sensitivity, 0.23 (95% CI, 0.20-0.25); I^2 = 47.4%; specificity, 0.96 (95% CI, 0.95-0.97); I^2 = 94.8 Estimates for sensitivity to detect CRC were slightly higher in studies using differential reference standard (registry follow-up)	Consistent, precise	Other than OC-Sensor and OC-Light, FITs were not evaluated in more than a single study using colonoscopy reference standards	High	Estimates apply to OC-Sensor family of FITs using manufacturer recommended cutoff[d] OC-Light has similar sensitivity and specificity to OC-Sensor Ten studies included people younger than 50 y No differences in test accuracy by age

(continued)

Table 5. Summary of Evidence (continued)

Instrument or treatment	Study design (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
sDNA	4 Studies, colonoscopy reference standard (n = 12 424)	CRC: Sensitivity, 0.93 (95% CI, 0.87-1.0); I^2 = 0%; specificity, 0.85 (95% CI, 0.84-0.86); I^2 = 37.7% Advanced adenoma: Sensitivity, 0.43 (95% CI, 0.40-0.46); I^2 = 0%); specificity, 0.89 (95% CI, 0.86-0.92); I^2 = 87.8%	Consistent, precise	Only 1 study adequately powered to detect cancers	Moderate	Estimates apply to Cologuard (sDNA-FIT) In the largest study, 6% of people had inadequate stool samples Two studies included people younger than 50 y
Serum test	1 Study, colonoscopy reference standard (n = 6857)	CRC: Sensitivity, 0.68 (95% CI, 0.53-0.80); specificity, 0.79 (95% CI, 0.77-0.81) Advanced adenoma: Sensitivity, 0.22 (95% CI, 0.18-0.24); specificity, 0.79 (95% CI, 0.76-0.82)	Consistency NA, precise	Single nested case-control study	Low	Estimates apply to Epi proColon, evaluating the m*SEPT9* marker Currently only FDA-approved for people unwilling or unable to be screened by gFOBT, FIT, flexible sigmoidoscopy, or colonoscopy Did not include people younger than 50 y
KQ3: Harms of screening						
Flexible sigmoidoscopy	18 Observational studies (n = 395 077)	Major bleeding: 0.5 (95% CI, 0-1.3) events per 10 000 procedures Perforation: 0.2 (95% CI, 0.1-0.4) events per 10 000 procedures Other serious harms: not routinely reported but cannot be attributed to flexible sigmoidoscopy procedure	Consistent, precise	No studies with control group (no flexible sigmoidoscopy) Possible reporting bias of harms other than bleeding and perforation	Moderate	Reflects community practice, but flexible sigmoidoscopy no longer widely used in US practice No studies included people younger than 50 y
Screening colonoscopy	67 Observational studies (n = 27 746 669)	Major bleeding: 14.6 (95% CI, 9.4-19.9) events per 10 000 procedures Perforation: 3.1 (95% CI, 2.3-4.0) events per 10 000 procedures Other serious harms: in 4 studies with comparator groups, similar or less frequent adverse events in screened vs unscreened group	Consistent, precise	Only 4 studies with unscreened comparison	Moderate	Reflects community practice Twenty-one studies included people younger than 50 y Risk of serious harms appears to increase with age
Colonoscopy after an abnormal CT colonography, flexible sigmoidoscopy, or stool test result	21 Observational studies (n = 903 872)	After abnormal stool test result: Major bleeding: 17.5 (95% CI, 7.6-27.5) events per 10 000 procedures Perforation: 5.4 (95% CI, 3.4-7.4) events per 10 000 procedures Other serious harms: No estimate After abnormal flexible sigmoidoscopy result: Major bleeding: 20.7 (95% CI, 8.2-33.2) events per 10 000 procedures Perforation: 12.0 (95% CI, 7.5-16.5) events per 10 000 procedures Other serious harms: No estimate	Consistent, precise	No studies with unscreened comparison	Moderate	Reflects community practice Two studies after abnormal stool testing included people younger than 50 y

(continued)

Table 5. Summary of Evidence (continued)

Instrument or treatment	Study design (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
CT colonography						
Harms	19 Observational studies (n = 90 133)	Serious harms from CT colonography in asymptomatic people are uncommon The effective dose of radiation per examination ranged from 0.8 to 5.3 mSv	Consistent, imprecise	No studies with control group (no CT colonography) More limited evidence in screening populations at true average risk Possible reporting bias of harms other than perforation	Moderate	Reflects community practice No studies included people younger than 50 y
ECF	27 Observational studies (n = 48 235)	ECFs requiring workup of potentially important findings (E4) occurred in 1.3% to 11.4% of examinations A minority of findings (≤3%) required definitive medical or surgical treatment, and extracolonic cancers were rarely detected (0.35%)	Consistent, imprecise	No studies able to quantify net benefit or harm Studies with varying levels of follow-up, few studies with final disposition of ECF	Low	ECF can be a benefit or a harm Prevalence of ECF appears to increase with age One study included people younger than 50 y

Abbreviations: CRC, colorectal cancer; CT, computed tomography; ECF, extracolonic finding; FDA, US Food and Drug Administration; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; HR, hazard ratio; IRR, incidence rate ratio; KQ, key question; m*SEPT9*, methylated septin 9 gene; NA, not applicable; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RCT, randomized clinical trial; RR, relative risk; sDNA, stool DNA.

[a] Several adequately powered comparative effectiveness studies are currently underway will evaluate the comparative effectiveness of direct visualization vs stool-based screening programs.

[b] CT colonography with bowel prep results, 7 studies (n = 5328).

[c] FN: OC-Sensor results, 13 studies (n = 44 597).

[d] At lower cutoffs (15 and 10 µg Hb/g feces), the sensitivity for CRC increased (0.92 and 0.99, respectively) and the corresponding specificities decreased (0.92 and 0.90, respectively).

Data from well-conducted population-based screening RCTs demonstrate that intention to screen with Hemoccult II or flexible sigmoidoscopy can reduce CRC mortality. Hemoccult II and flexible sigmoidoscopy, however, are no longer widely used for screening in the US. Newer screening tests with similar sensitivity may result in CRC mortality reductions similar to reductions shown in existing trials. If sensitivity is better, without a trade-off in specificity (eg, various FITs), mortality reductions could be greater.[275] Decision analyses can help understand the trade-offs of false-positive results and optimal intervals of testing for tests that maximize sensitivity with a reduction in specificity (eg, sDNA-FIT). To date, while serum testing has more limited evidence around test accuracy, it has better patient acceptability and adherence than stool-based testing.[276] While CT colonography has evidence to support the adequate detection for precursor lesions greater than or equal to 6 mm (similar to colonoscopy), it may have harms associated with the cumulative exposure of radiation with repeated examinations, the detection of incidental findings, or both.

Adherence to screening remains the biggest challenge to implementation of screening and has consistently lagged behind recommended screenings for other cancers.[277] Adherence to a single round of screening, repeated screening, and follow-up colonoscopy vary across studies, setting, and populations.[278] Differential adherence to screening tests influences the benefits and harms of screening program and may influence the selection of a preferred strategy.

Although the incidence of CRC has been increasing among adults younger than 50 years, there is little empirical evidence evaluating potential differences in the effectiveness of screening, test performance of screening tests, and the harms of screening in adults younger than 50 years. Any differences in the effectiveness of screening at younger ages would be attributable to varying the underlying risk or incidence of CRC, the natural history of disease, or both, as well as differences in test accuracy by age. Limited studies demonstrate no difference in test accuracy of stool testing or harms of colonoscopy in people younger than 50 years. Although it is not hypothesized that colonoscopy or CT colonography are more harmful in younger adults than older adults, initiating screening at an earlier age will accrue more procedural harms and extracolonic findings, which should be weighed against any incremental benefit of earlier start to screening.

Systematic reviews have identified multivariable risk prediction models with adequate discrimination,[279,280] many of which have been externally validated[281,282]; however, they are not commonly used in clinical practice.[279,283] In theory, multivariable risk assessment can identify persons at higher risk for CRC and tailor when to initiate screening.

While several CRC screening trials evaluating colonoscopy, CT colonography, and FIT are underway, future research should also include trials or well-designed cohort studies in average-risk populations to evaluate the effects of new serum- and urine-based tests on cancer mortality and incidence. In addition, future research should include adequate sampling of different populations (by age, family risk, and race/ethnicity) to allow for robust subgroup analyses, use multivariable risk assessment to guide screening, or both. Studies to confirm the screening test performance of FITs with thus-far limited reproducibility would be helpful to offer other FIT alternatives to OC-Sensor and OC-Light. Likewise, test accuracy studies adequately powered for cancer detection to establish or confirm the

screening test performance of promising serum- and urine-based tests are needed to bolster a menu of options for screening that may have greater acceptability and feasibility. In general test accuracy studies to clarify any differential in detection of proximal vs distal test accuracy, and the detection of precursor lesions with more potential for malignant transformation (eg, serrated sessile lesions), would also be informative. In addition, understanding the overall net effect of detection of extracolonic findings may be helped by reporting of the downstream benefits and harms of extracolonic findings in randomized or nonrandomized studies with longer-term follow-up.

Limitations

This review has several limitations. First, it excluded studies in symptomatic people and people with the highest hereditary risk. Second, it included only trials or prospective cohort studies designed to evaluate the association of screening with CRC incidence or mortality. It is possible that excluded well-designed nested case-control studies of colonoscopy or FIT may have lower risk of bias than included prospective cohort studies. Third, although this review addressed some important contextual issues related to screening (eg, adherence to testing, risk assessment to tailor screening, test acceptability and availability), it did not include an assessment of the mechanism of benefit of the different screening tests (primary prevention vs early detection), methods to increase screening adherence, prevalence of interval cancers between screenings, potential harms of overdetection of adenomas or unnecessary polypectomy, technological enhancements to improve the test accuracy of direct visualization, and surveillance after screening.

Conclusions

There are several options to screen for colorectal cancer, each with a different level of evidence demonstrating its ability to reduce cancer mortality, its ability to detect cancer or precursor lesions, and its risk of harms.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
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Critical revision of the manuscript for important intellectual content: Perdue, Henrikson, Blasi.
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REFERENCES

1. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(3):145-164. doi:10.3322/caac.21601

2. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974-2013. *J Natl Cancer Inst*. 2017;109(8):djw322. doi:10.1093/jnci/djw322

3. US Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008;149(9):627-637. doi:10.7326/0003-4819-149-9-200811040-00243

4. Lin JS, Piper MA, Perdue LA, et al. *Screening for Colorectal Cancer: A Systematic Review for the US Preventive Services Task Force. Evidence Synthesis No. 135*. Agency for Healthcare Research and Quality; 2016. AHRQ publication 14-05203-EF-1.

5. Lin JS, Piper MA, Perdue LA, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;315(23):2576-2594. doi:10.1001/jama.2016.3332

6. Knudsen AB, Rutter CM, Peterse EFP, et al. Colorectal cancer screening: an updated modeling study for the US Preventive Services Task Force. *JAMA*. Published May 18, 2021. doi:10.1001/jama.2021.5746

7. Knudsen AB, Rutter CM, Peterse EF, et al. *Colorectal Cancer Screening: A Decision Analysis for the US Preventive Services Task Force*. Agency for Healthcare Research and Quality; 2021. AHRQ publication 20-05271-EF-2.

8. Procedure Manual. US Preventive Services Task Force. Published 2018. Accessed March 10, 2021. https://uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual

9. Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. *Screening for Colorectal Cancer: An Evidence Update for the US Preventive Services Task Force. Evidence Synthesis No. 202*. Agency for Healthcare Research and Quality; 2021. AHRQ publication 20-05271-EF-1.

10. Randel KR, Schult AL, Botteri E, et al. Colorectal cancer screening with repeated fecal immunochemical test versus sigmoidoscopy: baseline results from a randomized trial. *Gastroenterology*. 2021;160(4):1085-1096. doi:10.1053/j.gastro.2020.11.037

11. Imperiale TF, Kisiel JB, Itzkowitz SH, et al. Specificity of the multi-target stool DNA test for colorectal cancer screening in average-risk 45-49 year-olds: a cross-sectional study. *Cancer Prev Res (Phila)*. 2021;14(4):489-496. doi:10.1158/1940-6207.CAPR-20-0294

12. Leeflang MM, Bossuyt PM, Irwig L. Diagnostic test accuracy may vary with prevalence: implications for evidence-based diagnosis. *J Clin Epidemiol*. 2009;62(1):5-12. doi:10.1016/j.jclinepi.2008.04.007

13. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA*. 1999;282(11):1061-1066. doi:10.1001/jama.282.11.1061

14. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med*. 1978;299(17):926-930. doi:10.1056/NEJM197810262991705

15. Rutjes AW, Reitsma JB, Di Nisio M, Smidt N, van Rijn JC, Bossuyt PM. Evidence of bias and variation in diagnostic accuracy studies. *CMAJ*. 2006;174(4):469-476. doi:10.1503/cmaj.050090

16. Whiting P, Rutjes AW, Reitsma JB, Glas AS, Bossuyt PM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. *Ann Intern Med*. 2004;140(3):189-202. doi:10.7326/0003-4819-140-3-200402030-00010

17. Berkman ND, Lohr KN, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: an update. In: Agency for Healthcare Research and Quality, eds. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Agency for Healthcare Research and Quality; 2014:314-349. AHRQ publication 10(14)-EHC063-EF.

18. Regge D, Iussich G, Segnan N, et al. Comparing CT colonography and flexible sigmoidoscopy: a randomised trial within a population-based screening programme. *Gut*. 2017;66(8):1434-1440. doi:10.1136/gutjnl-2015-311278

19. Holme Ø, Løberg M, Kalager M, et al; NORCCAP Study Group. Long-term effectiveness of sigmoidoscopy screening on colorectal cancer incidence and mortality in women and men: a randomized trial. *Ann Intern Med*. 2018;168(11):775-782. doi:10.7326/M17-1441

20. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. *N Engl J Med*. 2013;369(12):1106-1114. doi:10.1056/NEJMoa1300720

21. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. *Br J Surg*. 2008;95(8):1029-1036. doi:10.1002/bjs.6136

22. Verne JE, Aubrey R, Love SB, Talbot IC, Northover JM. Population based randomised study of uptake and yield of screening by flexible sigmoidoscopy compared with screening by faecal occult blood testing. *BMJ*. 1998;317(7152):182-185. doi:10.1136/bmj.317.7152.182

23. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncol*. 2012;13(1):55-64. doi:10.1016/S1470-2045(11)70283-2

24. Miller EA, Pinsky PF, Schoen RE, Prorok PC, Church TR. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: long-term follow-up of the randomised US PLCO cancer screening trial. *Lancet Gastroenterol Hepatol*. 2019;4(2):101-110. doi:10.1016/S2468-1253(18)30358-3

25. Rasmussen M, Kronborg O, Fenger C, Jørgensen OD. Possible advantages and drawbacks of adding flexible sigmoidoscopy to Hemoccult-II in screening for colorectal cancer: a randomized study. *Scand J Gastroenterol*. 1999;34(1):73-78. doi:10.1080/00365529950172862

26. Quintero E, Castells A, Bujanda L, et al; COLONPREV Study Investigators. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med*. 2012;366(8):697-706. doi:10.1056/NEJMoa1108895

27. Faivre J, Dancourt V, Lejeune C, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology*. 2004;126(7):1674-1680. doi:10.1053/j.gastro.2004.02.018

28. Brevinge H, Lindholm E, Buntzen S, Kewenter J. Screening for colorectal neoplasia with faecal occult blood testing compared with flexible sigmoidoscopy directly in a 55-56 years' old population. *Int J Colorectal Dis*. 1997;12(5):291-295. doi:10.1007/s003840050108

29. Atkin W, Wooldrage K, Parkin DM, et al. Long-term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet*. 2017;389(10076):1299-1311. doi:10.1016/S0140-6736(17)30396-3

30. Zubero MB, Arana-Arri E, Pijoan JI, et al. Population-based colorectal cancer screening: comparison of two fecal occult blood test. *Front Pharmacol*. 2014;4:175. doi:10.3389/fphar.2013.00175

31. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology*. 2008;135(1):82-90. doi:10.1053/j.gastro.2008.03.040

32. van Roon AH, Goede SL, van Ballegooijen M, et al. Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening. *Gut*. 2013;62(3):409-415. doi:10.1136/gutjnl-2011-301583

33. Segnan N, Senore C, Andreoni B, et al; SCORE3 Working Group–Italy. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. *Gastroenterology*. 2007;132(7):2304-2312. doi:10.1053/j.gastro.2007.03.030

34. Segnan N, Senore C, Andreoni B, et al; SCORE2 Working Group–Italy. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. *J Natl Cancer Inst*. 2005;97(5):347-357. doi:10.1093/jnci/dji050

35. Segnan N, Armaroli P, Bonelli L, et al; SCORE Working Group. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial—SCORE. *J Natl Cancer Inst*. 2011;103(17):1310-1322. Published correction appears in *J Natl Cancer Inst*. 2011;103(24):1903. doi:10.1093/jnci/djr284

36. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut*. 2012;61(7):1036-1040. doi:10.1136/gutjnl-2011-300774

37. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med*. 2013;369(12):1095-1105. doi:10.1056/NEJMoa1301969

38. Pitkäniemi J, Seppä K, Hakama M, et al. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. *BMJ Open Gastroenterol*. 2015;2(1):e000034. doi:10.1136/bmjgast-2015-000034

39. Kronborg O, Jørgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. *Scand J Gastroenterol*. 2004;39(9):846-851. doi:10.1080/00365520410003182

40. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut*. 2010;59(1):62-68. doi:10.1136/gut.2009.177089

41. Faivre J, Dancourt V, Denis B, et al. Comparison between a guaiac and three immunochemical faecal occult blood tests in screening for colorectal cancer. *Eur J Cancer*. 2012;48(16):2969-2976. doi:10.1016/j.ejca.2012.04.007

42. Berry DP, Clarke P, Hardcastle JD, Vellacott KD. Randomized trial of the addition of flexible sigmoidoscopy to faecal occult blood testing for colorectal neoplasia population screening. *Br J Surg*. 1997;84(9):1274-1276.

43. Sali L, Mascalchi M, Falchini M, et al. Reduced and full-preparation CT colonography, fecal immunochemical test, and colonoscopy for population screening of colorectal cancer: a randomized trial. *J Natl Cancer Inst*. Published December 30, 2015. doi:10.1093/jnci/djv319

44. Passamonti B, Malaspina M, Fraser CG, et al. A comparative effectiveness trial of two faecal immunochemical tests for haemoglobin (FIT): assessment of test performance and adherence in a single round of a population-based screening programme for colorectal cancer. *Gut*. 2018;67(3):485-496. doi:10.1136/gutjnl-2016-312716

45. Santare D, Kojalo I, Liepniece-Karele I, et al. Comparison of the yield from two faecal immunochemical tests at identical cutoff concentrations—a randomized trial in Latvia. *Eur J Gastroenterol Hepatol*. 2016;28(8):904-910. doi:10.1097/MEG.0000000000000650

46. Chiu HM, Chen SL, Yen AM, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. *Cancer*. 2015;121(18):3221-3229. doi:10.1002/cncr.29462

47. García-Albéniz X, Hsu J, Bretthauer M, Hernán MA. Effectiveness of screening colonoscopy to prevent colorectal cancer among Medicare beneficiaries aged 70 to 79 years: a prospective observational study. *Ann Intern Med*. 2017;166(1):18-26. doi:10.7326/M16-0758

48. Schreuders EH, Grobbee EJ, Nieuwenburg SAV, et al. Multiple rounds of one sample versus two sample faecal immunochemical test–based colorectal cancer screening: a population-based study. *Lancet Gastroenterol Hepatol*. 2019;4(8):622-631. doi:10.1016/S2468-1253(19)30176-1

49. Steele RJ, Carey FA, Stanners G, et al. Randomized controlled trial: flexible sigmoidoscopy as an adjunct to faecal occult blood testing in population screening. *J Med Screen*. 2020;27(2):59-67. doi:10.1177/0969141319879955

50. Grobbee EJ, van der Vlugt M, van Vuuren AJ, et al. Diagnostic yield of one-time colonoscopy vs one-time flexible sigmoidoscopy vs multiple rounds of mailed fecal immunohistochemical tests in colorectal cancer screening. *Clin Gastroenterol Hepatol*. 2020;18(3):667-675.

51. Segnan N, Senore C, Andreoni B, et al; SCORE Working Group—Italy. Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy"—SCORE. *J Natl Cancer Inst*. 2002;94(23):1763-1772. doi:10.1093/jnci/94.23.1763

52. Atkin WS, Cook CF, Cuzick J, Edwards R, Northover JM, Wardle J; UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet*. 2002;359(9314):1291-1300. Published correction appears in *Lancet*. 2010;375(9732):2142. doi:10.1016/S0140-6736(02)08268-5

53. Mandel JS, Bond JH, Church TR, et al; Minnesota Colon Cancer Control Study. Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med*. 1993;328(19):1365-1371. doi:10.1056/NEJM199305133281901

54. Weissfeld JL, Schoen RE, Pinsky PF, et al; PLCO Project Team. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. *J Natl Cancer Inst*. 2005;97(13):989-997. doi:10.1093/jnci/dji175

55. van Roon AH, Wilschut JA, Hol L, et al. Diagnostic yield improves with collection of 2 samples in fecal immunochemical test screening without affecting attendance. *Clin Gastroenterol Hepatol*. 2011;9(4):333-339. doi:10.1016/j.cgh.2010.12.012

56. Thomas W, White CM, Mah J, Geisser MS, Church TR, Mandel JS; Minnesota Colon Cancer Control Study. Longitudinal compliance with annual screening for fecal occult blood. *Am J Epidemiol*. 1995;142(2):176-182. doi:10.1093/oxfordjournals.aje.a117616

57. Parra-Blanco A, Nicolas-Perez D, Gimeno-Garcia A, et al. The timing of bowel preparation before colonoscopy determines the quality of cleansing, and is a significant factor contributing to the detection of flat lesions: a randomized study. *World J Gastroenterol*. 2006;12(38):6161-6166. doi:10.3748/wjg.v12.i38.6161

58. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med*. 2000;343(22):1603-1607. doi:10.1056/NEJM200011303432203

59. Malila N, Oivanen T, Malminiemi O, Hakama M. Test, episode, and programme sensitivities of screening for colorectal cancer as a public health policy in Finland: experimental design. *BMJ*. 2008;337:a2261. doi:10.1136/bmj.a2261

60. Kewenter J, Brevinge H, Engaras B, Haglind E, Ahrén C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing: results for 68,308 subjects. *Scand J Gastroenterol*. 1994;29(5):468-473. doi:10.3109/00365529409096840

61. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet*. 1996;348(9040):1472-1477. doi:10.1016/S0140-6736(96)03386-7

62. Faivre J, Dancourt V, Manfredi S, et al. Positivity rates and performances of immunochemical faecal occult blood tests at different cut-off levels within a colorectal cancer screening programme. *Dig Liver Dis*. 2012;44(8):700-704. doi:10.1016/j.dld.2012.03.015

63. Denters MJ, Deutekom M, Fockens P, Bossuyt PM, Dekker E. Implementation of population screening for colorectal cancer by repeated fecal occult blood test in the Netherlands. *BMC Gastroenterol*. 2009;9:28. doi:10.1186/1471-230X-9-28

64. Miles A, Wardle J, McCaffery K, Williamson S, Atkin W. The effects of colorectal cancer screening on health attitudes and practices. *Cancer Epidemiol Biomarkers Prev*. 2003;12(7):651-655.

65. Atkin WS, Edwards R, Kralj-Hans I, et al; UK Flexible Sigmoidoscopy Trial Investigators. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet*. 2010;375(9726):1624-1633. doi:10.1016/S0140-6736(10)60551-X

66. Koskenvuo L, Malila N, Pitkäniemi J, Miettinen J, Heikkinen S, Sallinen V. Sex differences in faecal occult blood test screening for colorectal cancer. *Br J Surg*. 2019;106(4):436-447. doi:10.1002/bjs.11011

67. Kapidzic A, van Roon AH, van Leerdam ME, et al. Attendance and diagnostic yield of repeated two-sample faecal immunochemical test screening for colorectal cancer. *Gut*. 2017;66(1):118-123. doi:10.1136/gutjnl-2014-308957

68. Doroudi M, Schoen RE, Pinsky PF. Early detection versus primary prevention in the PLCO flexible sigmoidoscopy screening trial: which has the greatest impact on mortality? *Cancer*. 2017;123(24):4815-4822. doi:10.1002/cncr.31034

69. Schoen RE, Pinsky PF, Weissfeld JL, et al; PLCO Project Team. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med*. 2012;366(25):2345-2357. doi:10.1056/NEJMoa1114635

70. Malila N, Palva T, Malminiemi O, et al. Coverage and performance of colorectal cancer screening with the faecal occult blood test in Finland. *J Med Screen*. 2011;18(1):18-23. doi:10.1258/jms.2010.010036

71. Senore C, Correale L, Regge D, et al. Flexible sigmoidoscopy and CT colonography screening: patients' experience with and factors for undergoing screening—insight from the Proteus Colon Trial. *Radiology*. 2018;286(3):873-883. doi:10.1148/radiol.2017170228

72. Castells A, Quintero E. Programmatic screening for colorectal cancer: the COLONPREV study. *Dig Dis Sci*. 2015;60(3):672-680. doi:10.1007/s10620-014-3446-2

73. Schoen RE, Razzak A, Yu KJ, et al. Incidence and mortality of colorectal cancer in individuals with a family history of colorectal cancer. *Gastroenterology*. 2015;149(6):1438-1445. doi:10.1053/j.gastro.2015.07.055

74. Holme Ø, Løberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. *JAMA*. 2014;312(6):606-615. doi:10.1001/jama.2014.8266

75. Holme Ø, Bretthauer M, Eide TJ, et al. Long-term risk of colorectal cancer in individuals with serrated polyps. *Gut*. 2015;64(6):929-936. doi:10.1136/gutjnl-2014-307793

76. Jodal HC, Loberg M, Holme O, et al. Mortality from postscreening (interval) colorectal cancers is comparable to that from cancer in unscreened patients—a randomized sigmoidoscopy trial. *Gastroenterology*. 2018;155(6):1787-1794. doi:10.1053/j.gastro.2018.08.035

77. Laiyemo AO, Doubeni C, Pinsky PF, et al. Occurrence of distal colorectal neoplasia among whites and blacks following negative flexible sigmoidoscopy: an analysis of PLCO trial. *J Gen Intern Med*. 2015;30(10):1447-1453. doi:10.1007/s11606-015-3297-3

78. Gondal G, Grotmol T, Hofstad B, Bretthauer M, Eide TJ, Hoff G. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. *Scand J Gastroenterol*. 2003;38(6):635-642. doi:10.1080/00365520310003002

79. Hoff G, Grotmol T, Skovlund E, Bretthauer M; Norwegian Colorectal Cancer Prevention Study Group. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. *BMJ*. 2009;338:b1846. doi:10.1136/bmj.b1846

80. Kewenter J, Brevinge H. Endoscopic and surgical complications of work-up in screening for colorectal cancer. *Dis Colon Rectum*. 1996;39(6):676-680. doi:10.1007/BF02056949

81. Dube C, Tinmouth J. Number of samples in faecal immunochemical test screening: more might be less. *Lancet Gastroenterol Hepatol*. 2019;4(8):577-578. doi:10.1016/S2468-1253(19)30191-8

82. Pinsky P, Miller E, Zhu C, Prorok P. Overall mortality in men and women in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *J Med Screen*. 2019;26(3):127-134. doi:10.1177/0969141319839097

83. Grobbee EJ, van der Vlugt M, van Vuuren AJ, et al. A randomised comparison of two faecal immunochemical tests in population-based colorectal cancer screening. *Gut*. 2017;66(11):1975-1982. doi:10.1136/gutjnl-2016-311819

84. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. *Ann Intern Med*. 2008;149(7):441-450. doi:10.7326/0003-4819-149-7-200810070-00004

85. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med*. 1996;334(3):155-159. doi:10.1056/NEJM199601183340304

86. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. *J Natl Cancer Inst*. 2007;99(19):1462-1470. doi:10.1093/jnci/djm150

87. Arana-Arri E, Idigoras I, Uranga B, et al; EUSKOLON Group. Population-based colorectal cancer screening programmes using a faecal immunochemical test: should faecal haemoglobin cut-offs differ by age and sex? *BMC Cancer*. 2017;17(1):577. doi:10.1186/s12885-017-3555-3

88. Brenner H, Chen H. Fecal occult blood versus DNA testing: indirect comparison in a colorectal

cancer screening population. *Clin Epidemiol*. 2017; 9:377-384. doi:10.2147/CLEP.S136565

89. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. *Eur J Cancer*. 2013;49(14):3049-3054. doi:10.1016/j.ejca.2013.04.023

90. Castiglione G, Visioli CB, Ciatto S, et al. Sensitivity of latex agglutination faecal occult blood test in the Florence District population-based colorectal cancer screening programme. *Br J Cancer*. 2007;96(11):1750-1754. doi:10.1038/sj.bjc.6603759

91. Chang LC, Shun CT, Hsu WF, et al. Fecal immunochemical test detects sessile serrated adenomas and polyps with a low level of sensitivity. *Clin Gastroenterol Hepatol*. 2017;15(6):872-879.e1. doi:10.1016/j.cgh.2016.07.029

92. Chen CH, Wen CP, Tsai MK. Fecal immunochemical test for colorectal cancer from a prospective cohort with 513,283 individuals: providing detailed number needed to scope (NNS) before colonoscopy. *Medicine (Baltimore)*. 2016;95 (36):e4414. doi:10.1097/MD.0000000000004414

93. Chen LS, Yen AM, Chiu SY, Liao CS, Chen HH. Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. *Lancet Oncol*. 2011;12(6):551-558. doi:10.1016/S1470-2045(11)70101-2

94. Chen SL, Hsu CY, Yen AM, et al. Demand for colonoscopy in colorectal cancer screening using a quantitative fecal immunochemical test and age/sex-specific thresholds for test positivity. *Cancer Epidemiol Biomarkers Prev*. 2018;27(6):704-709. doi:10.1158/1055-9965.EPI-17-0387

95. Chen Y-Y, Chen T-H, Su M-Y, et al. Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups. *Adv Digest Med*. 2014;1(3):74-79. doi:10.1016/j.aidm.2013.09.003

96. Cheng TI, Wong JM, Hong CF, et al. Colorectal cancer screening in asymptomaic adults: comparison of colonoscopy, sigmoidoscopy and fecal occult blood tests. *J Formos Med Assoc*. 2002; 101(10):685-690.

97. Chiu HM, Ching JY, Wu KC, et al; Asia-Pacific Working Group on Colorectal Cancer. A risk-scoring system combined with a fecal immunochemical test is effective in screening high-risk subjects for early colonoscopy to detect advanced colorectal neoplasms. *Gastroenterology*. 2016;150(3):617-625. doi:10.1053/j.gastro.2015.11.042

98. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. *Clin Gastroenterol Hepatol*. 2013;11(7):832-8.e1, 2. doi:10.1016/j.cgh.2013.01.013

99. Cooper GS, Markowitz SD, Chen Z, et al. Performance of multitarget stool DNA testing in African American patients. *Cancer*. 2018;124(19): 3876-3880. doi:10.1002/cncr.31660

100. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. *Am J Gastroenterol*. 2012;107(10):1570-1578. doi:10.1038/ajg.2012.249

101. Deng L, Chang D, Foshaug RR, et al. Development and validation of a high-throughput mass spectrometry based urine metabolomic test for the detection of colonic adenomatous polyps. *Metabolites*. 2017;7(3):22. doi:10.3390/metabo7030032

102. Fletcher JG, Silva AC, Fidler JL, et al. Noncathartic CT colonography: image quality assessment and performance and in a screening cohort. *AJR Am J Roentgenol*. 2013;201(4):787-794. doi:10.2214/AJR.12.9225

103. Garcia M, Domènech X, Vidal C, et al. Interval cancers in a population-based screening program for colorectal cancer in Catalonia, Spain. *Gastroenterol Res Pract*. 2015;2015:672410. doi:10.1155/2015/672410

104. Gies A, Cuk K, Schrotz-King P, Brenner H. Direct comparison of diagnostic performance of 9 quantitative fecal immunochemical tests for colorectal cancer screening. *Gastroenterology*. 2018;154(1):93-104. doi:10.1053/j.gastro.2017.09.018

105. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. *Gut*. 2009;58(2):241-248. doi:10.1136/gut.2008.156448

106. Haug U, Grobbee EJ, Lansdorp-Vogelaar I, Spaander MCW, Kuipers EJ. Immunochemical faecal occult blood testing to screen for colorectal cancer: can the screening interval be extended? *Gut*. 2017; 66(7):1262-1267. doi:10.1136/gutjnl-2015-310102

107. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al; COLONPREV Study Investigators. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. *World J Gastroenterol*. 2014;20(4):1038-1047. doi:10.3748/wjg.v20.i4.1038

108. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. 2014; 370(14):1287-1297. doi:10.1056/NEJMoa1311194

109. Itoh M, Takahashi K, Nishida H, Sakagami K, Okubo T. Estimation of the optimal cut off point in a new immunological faecal occult blood test in a corporate colorectal cancer screening programme. *J Med Screen*. 1996;3(2):66-71. doi:10.1177/096914139600300204

110. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med*. 2008;359 (12):1207-1217. doi:10.1056/NEJMoa0800996

111. Johnson CD, Fletcher JG, MacCarty RL, et al. Effect of slice thickness and primary 2D versus 3D virtual dissection on colorectal lesion detection at CT colonography in 452 asymptomatic adults. *AJR Am J Roentgenol*. 2007;189(3):672-680. doi:10.2214/AJR.07.2354

112. Juul JS, Andersen B, Laurberg S, Carlsen AH, Olesen F, Vedsted P. Differences in diagnostic activity in general practice and findings for individuals invited to the danish screening programme for colorectal cancer: a population-based cohort study. *Scand J Prim Health Care*. 2018;36(3):281-290. doi:10.1080/02813432.2018.1487378

113. Kim NH, Park JH, Park DI, Sohn CI, Choi K, Jung YS. The fecal immunochemical test has high accuracy for detecting advanced colorectal neoplasia before age 50. *Dig Liver Dis*. 2017;49(5): 557-561. doi:10.1016/j.dld.2016.12.020

114. Kim YS, Kim N, Kim SH, et al. The efficacy of intravenous contrast-enhanced 16-raw multidetector CT colonography for detecting patients with colorectal polyps in an asymptomatic population in Korea. *J Clin Gastroenterol*. 2008;42 (7):791-798. doi:10.1097/MCG.0b013e31811edcb7

115. Launoy GD, Bertrand HJ, Berchi C, et al. Evaluation of an immunochemical fecal occult blood test with automated reading in screening for colorectal cancer in a general average-risk population. *Int J Cancer*. 2005;115(3):493-496. doi:10.1002/ijc.20921

116. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. *Clin Chem Lab Med*. 2015;53(3):e69-e71. doi:10.1515/cclm-2014-0442

117. Lefere P, Silva C, Gryspeerdt S, et al. Teleradiology based CT colonography to screen a population group of a remote island at average risk for colorectal cancer. *Eur J Radiol*. 2013;82(6):e262-e267. doi:10.1016/j.ejrad.2013.02.010

118. Levi Z, Birkenfeld S, Vilkin A, et al. A higher detection rate for colorectal cancer and advanced adenomatous polyp for screening with immunochemical fecal occult blood test than guaiac fecal occult blood test, despite lower compliance rate: prospective, controlled, feasibility study. *Int J Cancer*. 2011;128(10):2415-2424. doi:10.1002/ijc.25574

119. Levy BT, Bay C, Xu Y, et al. Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. *J Med Screen*. 2014;21(3): 133-143. doi:10.1177/0969141314541109

120. Liles EG, Perrin N, Rosales AG, et al. Performance of a quantitative fecal immunochemical test for detecting advanced colorectal neoplasia: a prospective cohort study. *BMC Cancer*. 2018;18(1):509. doi:10.1186/s12885-018-4402-x

121. Macari M, Bini EJ, Jacobs SL, et al. Colorectal polyps and cancers in asymptomatic average-risk patients: evaluation with CT colonography. *Radiology*. 2004;230(3):629-636. doi:10.1148/radiol.2303021624

122. Mlakar DN, Bric TK, Škrjanec AL, Krajc M. Interval cancers after negative immunochemical test compared to screen and non-responders' detected cancers in Slovenian colorectal cancer screening programme. *Radiol Oncol*. 2018;52(4): 413-421. doi:10.2478/raon-2018-0025

123. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology*. 2005;129(2):422-428. doi:10.1016/j.gastro.2005.05.056

124. Nakama H, Kamijo N, Abdul Fattah AS, Zhang B. Validity of immunological faecal occult blood screening for colorectal cancer: a follow up study. *J Med Screen*. 1996;3(2):63-65. doi:10.1177/096914139600300203

125. Nakama H, Yamamoto M, Kamijo N, et al. Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal

neoplasia. *Hepatogastroenterology*. 1999;46(25):228-231.

126. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. *Aliment Pharmacol Ther*. 2013;38(7):835-841. doi:10.1111/apt.12446

127. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. *Am J Gastroenterol*. 2010;105(9):2017-2025. doi:10.1038/ajg.2010.179

128. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med*. 2003;349(23):2191-2200. doi:10.1056/NEJMoa031618

129. Potter NT, Hurban P, White MN, et al. Validation of a real-time PCR-based qualitative assay for the detection of methylated *SEPT9* DNA in human plasma. *Clin Chem*. 2014;60(9):1183-1191. doi:10.1373/clinchem.2013.221044

130. Redwood DG, Asay ED, Blake ID, et al. Stool DNA testing for screening detection of colorectal neoplasia in Alaska Native people. *Mayo Clin Proc*. 2016;91(1):61-70. doi:10.1016/j.mayocp.2015.10.008

131. Rex DK, Adler SN, Aisenberg J, et al. Accuracy of capsule colonoscopy in detecting colorectal polyps in a screening population. *Gastroenterology*. 2015;148(5):948-957. doi:10.1053/j.gastro.2015.01.025

132. Selby K, Jensen CD, Lee JK, et al. Influence of varying quantitative fecal immunochemical test positivity thresholds on colorectal cancer detection: a community-based cohort study. *Ann Intern Med*. 2018;169(7):439-447. doi:10.7326/M18-0244

133. Shapiro JA, Bobo JK, Church TR, et al. A comparison of fecal immunochemical and high-sensitivity guaiac tests for colorectal cancer screening. *Am J Gastroenterol*. 2017;112(11):1728-1735. doi:10.1038/ajg.2017.285

134. Sohn DK, Jeong SY, Choi HS, et al. Single immunochemical fecal occult blood test for detection of colorectal neoplasia. *Cancer Res Treat*. 2005;37(1):20-23. doi:10.4143/crt.2005.37.1.20

135. Stegeman I, van Doorn SC, Mundt MW, et al. Participation, yield, and interval carcinomas in three rounds of biennial FIT-based colorectal cancer screening. *Cancer Epidemiol*. 2015;39(3):388-393. doi:10.1016/j.canep.2015.03.012

136. van der Vlugt M, Grobbee EJ, Bossuyt PMM, et al. Interval colorectal cancer incidence among subjects undergoing multiple rounds of fecal immunochemical testing. *Gastroenterology*. 2017;153(2):439-447. doi:10.1053/j.gastro.2017.05.004

137. Wong MC, Ching JY, Chan VC, et al. Diagnostic accuracy of a qualitative fecal immunochemical test varies with location of neoplasia but not number of specimens. *Clin Gastroenterol Hepatol*. 2015;13(8):1472-1479. doi:10.1016/j.cgh.2015.02.021

138. Zalis ME, Blake MA, Cai W, et al. Diagnostic accuracy of laxative-free computed tomographic colonography for detection of adenomatous polyps in asymptomatic adults: a prospective evaluation. *Ann Intern Med*. 2012;156(10):692-702. doi:10.7326/0003-4819-156-10-201205150-00005

139. Ribbing Wilén H, Blom J, Höijer J, Andersson G, Löwbeer C, Hultcrantz R. Fecal immunochemical test in cancer screening—colonoscopy outcome in FIT positives and negatives. *Scand J Gastroenterol*. 2019;54(3):303-310. doi:10.1080/00365521.2019.1585569

140. Voska M, Zavoral M, Grega T, et al. Accuracy of colon capsule endoscopy for colorectal neoplasia detection in individuals referred for a screening colonoscopy. *Gastroenterol Res Pract*. 2019;2019:5975438. doi:10.1155/2019/5975438

141. Toes-Zoutendijk E, Kooyker AI, Dekker E, et al. Incidence of interval colorectal cancer after negative results from first-round fecal immunochemical screening tests, by cutoff value and participant sex and age. *Clin Gastroenterol Hepatol*. 2020;18(7):1493-1500. doi:10.1016/j.cgh.2019.08.021

142. Bosch LJW, Melotte V, Mongera S, et al. Multitarget stool DNA test performance in an average-risk colorectal cancer screening population. *Am J Gastroenterol*. 2019;114(12):1909-1918. doi:10.14309/ajg.0000000000000445

143. Johnson CD, Herman BA, Chen MH, et al. The National CT Colonography Trial: assessment of accuracy in participants 65 years of age and older. *Radiology*. 2012;263(2):401-408. doi:10.1148/radiol.12102177

144. Morikawa T, Kato J, Yamaji Y, et al. Sensitivity of immunochemical fecal occult blood test to small colorectal adenomas. *Am J Gastroenterol*. 2007;102(10):2259-2264. doi:10.1111/j.1572-0241.2007.01404.x

145. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. *Ann Intern Med*. 2009;150(3):162-169. doi:10.7326/0003-4819-150-3-200902030-00005

146. Haug U, Kuntz KM, Knudsen AB, Hundt S, Brenner H. Sensitivity of immunochemical faecal occult blood testing for detecting left- vs right-sided colorectal neoplasia. *Br J Cancer*. 2011;104(11):1779-1785. doi:10.1038/bjc.2011.160

147. Grazzini G, Castiglione G, Ciabattoni C, et al. Colorectal cancer screening programme by faecal occult blood test in Tuscany: first round results. *Eur J Cancer Prev*. 2004;13(1):19-26. doi:10.1097/00008469-200402000-00004

148. Brenner H, Haug U, Hundt S. Inter-test agreement and quantitative cross-validation of immunochromatographical fecal occult blood tests. *Int J Cancer*. 2010;127(7):1643-1649. doi:10.1002/ijc.25154

149. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. *Am J Gastroenterol*. 2010;105(11):2457-2464. doi:10.1038/ajg.2010.301

150. Chiang TH, Chuang SL, Chen SL, et al. Difference in performance of fecal immunochemical tests with the same hemoglobin cutoff concentration in a nationwide colorectal cancer screening program. *Gastroenterology*. 2014;147(6):1317-1326. doi:10.1053/j.gastro.2014.08.043

151. Wang H, Tso V, Wong C, Sadowski D, Fedorak RN. Development and validation of a highly sensitive urine-based test to identify patients with colonic adenomatous polyps. *Clin Transl Gastroenterol*. 2014;5:e54. doi:10.1038/ctg.2014.2

152. Gies A, Cuk K, Schrotz-King P, Brenner H. Combination of different fecal immunochemical tests in colorectal cancer screening: any gain in diagnostic performance? *Cancers (Basel)*. 2019;11(1):20. doi:10.3390/cancers11010120

153. Gies A, Cuk K, Schrotz-King P, Brenner H. Fecal immunochemical test for hemoglobin in combination with fecal transferrin in colorectal cancer screening. *United European Gastroenterol J*. 2018;6(8):1223-1231. doi:10.1177/2050640618784053

154. Chen H, Werner S, Brenner H. Fresh vs frozen samples and ambient temperature have little effect on detection of colorectal cancer or adenomas by a fecal immunochemical test in a colorectal cancer screening cohort in Germany. *Clin Gastroenterol Hepatol*. 2017;15(10):1547-1556. doi:10.1016/j.cgh.2016.10.018

155. Brenner H, Qian J, Werner S. Variation of diagnostic performance of fecal immunochemical testing for hemoglobin by sex and age: results from a large screening cohort. *Clin Epidemiol*. 2018;10:381-389. doi:10.2147/CLEP.S155548

156. Niedermaier T, Weigl K, Hoffmeister M, Brenner H. Diagnostic performance of one-off flexible sigmoidoscopy with fecal immunochemical testing in a large screening population. *Epidemiology*. 2018;29(3):397-406. doi:10.1097/EDE.0000000000000795

157. Grobbee EJ, Wieten E, Hansen BE, et al. Fecal immunochemical test-based colorectal cancer screening: the gender dilemma. *United European Gastroenterol J*. 2017;5(3):448-454. doi:10.1177/2050640616659998

158. Jung YS, Park CH, Kim NH, Park JH, Park DI, Sohn CI. Identifying the optimal strategy for screening of advanced colorectal neoplasia. *J Gastroenterol Hepatol*. 2017;32(5):1003-1010. doi:10.1111/jgh.13634

159. Brenner H, Werner S. Selecting a cut-off for colorectal cancer screening with a fecal immunochemical test. *Clin Transl Gastroenterol*. 2017;8(8):e111. doi:10.1038/ctg.2017.37

160. Brenner H, Niedermaier T, Chen H. Strong subsite-specific variation in detecting advanced adenomas by fecal immunochemical testing for hemoglobin. *Int J Cancer*. 2017;140(9):2015-2022. doi:10.1002/ijc.30629

161. Church TR, Wandell M, Lofton-Day C, et al; PRESEPT Clinical Study Steering Committee, Investigators and Study Team. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. *Gut*. 2014;63(2):317-325. doi:10.1136/gutjnl-2012-304149

162. Summary of Safety and Effectiveness Data for Cologuard. US Food and Drug Administration. Published 2014. Accessed August 1, 2019. https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130017b.pdf

163. Ferlitsch M, Reinhart K, Pramhas S, et al. Sex-specific prevalence of adenomas, advanced adenomas, and colorectal cancer in individuals undergoing screening colonoscopy. *JAMA*. 2011;306(12):1352-1358. doi:10.1001/jama.2011.1362

164. Bretthauer M, Kaminski MF, Løberg M, et al; Nordic-European Initiative on Colorectal Cancer (NordICC) Study Group. Population-based colonoscopy screening for colorectal cancer: a randomized clinical trial. *JAMA Intern Med*. 2016;

176(7):894-902. doi:10.1001/jamainternmed.2016.0960

165. Taya M, McHargue C, Ricci ZJ, Flusberg M, Weinstein S, Yee J. Comparison of extracolonic findings and clinical outcomes in a screening and diagnostic CT colonography population. *Abdom Radiol (NY)*. 2019;44(2):429-437. doi:10.1007/s00261-018-1753-3

166. Laanani M, Coste J, Blotière PO, Carbonnel F, Weill A. Patient, procedure, and endoscopist risk factors for perforation, bleeding, and splenic injury after colonoscopies. *Clin Gastroenterol Hepatol*. 2019;17(4):719-727. doi:10.1016/j.cgh.2018.08.005

167. Moreno CC, Fibus TF, Krupinski EA, Kim DH, Pickhardt PJ. Addressing racial disparity in colorectal cancer screening with CT colonography: experience in an African-American cohort. *Clin Colorectal Cancer*. 2018;17(2):e363-e367. doi:10.1016/j.clcc.2018.02.007

168. Zwink N, Holleczek B, Stegmaier C, Hoffmeister M, Brenner H. Complication rates in colonoscopy screening for cancer. *Dtsch Arztebl Int*. 2017;114(18):321-327. doi:10.3238/arztebl.2017.0321

169. Saraste D, Martling A, Nilsson PJ, et al. Complications after colonoscopy and surgery in a population-based colorectal cancer screening programme. *J Med Screen*. 2016;23(3):135-140. doi:10.1177/0969141315625701

170. Larson ME, Pickhardt PJ. CT colonography screening in extracolonic cancer survivors: impact on rates of colorectal and extracolonic findings by cancer type. *Abdom Radiol (NY)*. 2019;44(1):31-40. doi:10.1007/s00261-018-1708-8

171. Grossberg LB, Vodonos A, Papamichael K, Novack V, Sawhney M, Leffler DA. Predictors of post-colonoscopy emergency department use. *Gastrointest Endosc*. 2018;87(2):517-525. doi:10.1016/j.gie.2017.08.019

172. Kubisch CH, Crispin A, Mansmann U, Goke B, Kolligs FT. Screening for colorectal cancer is associated with lower disease stage: a population-based study. *Clin Gastroenterol Hepatol*. 2016;14(11):1612-1618. doi:10.1016/j.cgh.2016.04.008

173. Ibáñez J, Vanaclocha-Espí M, Pérez-Sanz E, et al; Grupo de Trabajo del Programa de Prevención de Cáncer Colorrectal de la Comunitat Valenciana; Grupo de Trabajo del Programa de Prevención de Cáncer Colorrectal de la Comunitat Valenciana (España). Severe complications in colorectal cancer screening colonoscopies in the Valencian Community. Article in Spanish. *Gastroenterol Hepatol*. 2018;41(9):553-561.

174. Wang L, Mannalithara A, Singh G, Ladabaum U. Low rates of gastrointestinal and non-gastrointestinal complications for screening or surveillance colonoscopies in a population-based study. *Gastroenterology*. 2018;154(3):540-555. doi:10.1053/j.gastro.2017.10.006

175. Mikkelsen EM, Thomsen MK, Tybjerg J, et al. Colonoscopy-related complications in a nationwide immunochemical fecal occult blood test-based colorectal cancer screening program. *Clin Epidemiol*. 2018;10:1649-1655. doi:10.2147/CLEP.S181204

176. Binefa G, Garcia M, Milà N, et al. Colorectal Cancer Screening Programme in Spain: results of key performance indicators after five rounds (2000-2012). *Sci Rep*. 2016;6:19532. doi:10.1038/srep19532

177. Rim JH, Youk T, Kang JG, et al. Fecal occult blood test results of the national colorectal cancer screening program in South Korea (2006-2013). *Sci Rep*. 2017;7(1):2804. doi:10.1038/s41598-017-03134-9

178. Pooler BD, Kim DH, Pickhardt PJ. Potentially important extracolonic findings at screening CT colonography: incidence and outcomes data from a clinical screening program. *AJR Am J Roentgenol*. 2016;206(2):313-318. doi:10.2214/AJR.15.15193

179. Forsberg A, Hammar U, Ekbom A, Hultcrantz R. A register-based study: adverse events in colonoscopies performed in Sweden 2001-2013. *Scand J Gastroenterol*. 2017;52(9):1042-1047. doi:10.1080/00365521.2017.1334812

180. Bielawska B, Hookey LC, Sutradhar R, et al. Anesthesia assistance in outpatient colonoscopy and risk of aspiration pneumonia, bowel perforation, and splenic injury. *Gastroenterology*. 2018;154(1):77-85. doi:10.1053/j.gastro.2017.08.043

181. Derbyshire E, Hungin P, Nickerson C, Rutter MD. Colonoscopic perforations in the English National Health Service Bowel Cancer Screening Programme. *Endoscopy*. 2018;50(9):861-870. doi:10.1055/a-0584-7138

182. Johnson DA, Lieberman D, Inadomi JM, et al. Increased post-procedural non-gastrointestinal adverse events after outpatient colonoscopy in high-risk patients. *Clin Gastroenterol Hepatol*. 2017;15(6):883-891. doi:10.1016/j.cgh.2016.12.015

183. Chukmaitov A, Siangphoe U, Dahman B, Bradley CJ, BouHaidar D. Patient comorbidity and serious adverse events after outpatient colonoscopy: population-based study from three states, 2006 to 2009. *Dis Colon Rectum*. 2016;59(7):677-687. doi:10.1097/DCR.0000000000000603

184. Hoff G, de Lange T, Bretthauer M, et al. Patient-reported adverse events after colonoscopy in Norway. *Endoscopy*. 2017;49(8):745-753. doi:10.1055/s-0043-105265

185. Wang P, Xu T, Ngamruengphong S, Makary MA, Kalloo A, Hutfless S. Rates of infection after colonoscopy and osophagogastroduodenoscopy in ambulatory surgery centres in the USA. *Gut*. 2018;67(9):1626-1636. doi:10.1136/gutjnl-2017-315308

186. Polter DE. Risk of colon perforation during colonoscopy at Baylor University Medical Center. *Proc (Bayl Univ Med Cent)*. 2015;28(1):3-6. doi:10.1080/08998280.2015.11929170

187. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. *Ann Intern Med*. 2009;150(12):849-857. doi:10.7326/0003-4819-150-12-200906160-00008

188. Rutter CM, Johnson E, Miglioretti DL, Mandelson MT, Inadomi J, Buist DS. Adverse events after screening and follow-up colonoscopy. *Cancer Causes Control*. 2012;23(2):289-296. doi:10.1007/s10552-011-9878-5

189. Zafar HM, Harhay MO, Yang J, Armstron K. Adverse events following computed tomographic colonography compared to optical colonoscopy in the elderly. *Prev Med Rep*. 2014;1:3-8. doi:10.1016/j.pmedr.2014.08.001

190. Iafrate F, Iussich G, Correale L, et al. Adverse events of computed tomography colonography: an Italian National Survey. *Dig Liver Dis*. 2013;45(8):645-650. doi:10.1016/j.dld.2013.02.020

191. Stock C, Ihle P, Sieg A, Schubert I, Hoffmeister M, Brenner H. Adverse events requiring hospitalization within 30 days after outpatient screening and nonscreening colonoscopies. *Gastrointest Endosc*. 2013;77(3):419-429. doi:10.1016/j.gie.2012.10.028

192. Sagawa T, Kakizaki S, Iizuka H, et al. Analysis of colonoscopic perforations at a local clinic and a tertiary hospital. *World J Gastroenterol*. 2012;18(35):4898-4904. doi:10.3748/wjg.v18.i35.4898

193. Hsieh TK, Hung L, Kang FC, Lan KM, Poon PW, So EC. Anesthesia does not increase the rate of bowel perforation during colonoscopy: a retrospective study. *Acta Anaesthesiol Taiwan*. 2009;47(4):162-166. doi:10.1016/S1875-4597(09)60049-7

194. Chukmaitov A, Bradley CJ, Dahman B, Siangphoe U, Warren JL, Klabunde CN. Association of polypectomy techniques, endoscopist volume, and facility type with colonoscopy complications. *Gastrointest Endosc*. 2013;77(3):436-446. doi:10.1016/j.gie.2012.11.012

195. Rabeneck L, Paszat LF, Hilsden RJ, et al. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. *Gastroenterology*. 2008;135(6):1899-1906, 1906.e1. doi:10.1053/j.gastro.2008.08.058

196. Sosna J, Blachar A, Amitai M, et al. Colonic perforation at CT colonography: assessment of risk in a multicenter large cohort. *Radiology*. 2006;239(2):457-463. doi:10.1148/radiol.2392050287

197. Kamath AS, Iqbal CW, Sarr MG, et al. Colonoscopic splenic injuries: incidence and management. *J Gastrointest Surg*. 2009;13(12):2136-2140. doi:10.1007/s11605-009-1064-7

198. Singh H, Penfold RB, DeCoster C, et al. Colonoscopy and its complications across a Canadian regional health authority. *Gastrointest Endosc*. 2009;69(3, pt 2):665-671. doi:10.1016/j.gie.2008.09.046

199. Rathgaber SW, Wick TM. Colonoscopy completion and complication rates in a community gastroenterology practice. *Gastrointest Endosc*. 2006;64(4):556-562. doi:10.1016/j.gie.2006.03.014

200. Pickhardt PJ, Kim DH, Meiners RJ, et al. Colorectal and extracolonic cancers detected at screening CT colonography in 10,286 asymptomatic adults. *Radiology*. 2010;255(1):83-88. doi:10.1148/radiol.09090939

201. Cotterill M, Gasparelli R, Kirby E. Colorectal cancer detection in a rural community: development of a colonoscopy screening program. *Can Fam Physician*. 2005;51:1224-1228.

202. Edwards JT, Mendelson RM, Fritschi L, et al. Colorectal neoplasia screening with CT colonography in average-risk asymptomatic subjects: community-based study. *Radiology*. 2004;230(2):459-464. doi:10.1148/radiol.2302021422

203. Multicentre Australian Colorectal-Neoplasia Screening (MACS) Group. A comparison of colorectal neoplasia screening tests: a multicentre community-based study of the impact of consumer choice. *Med J Aust*. 2006;184(11):546-550. doi:10.5694/j.1326-5377.2006.tb00377.x

204. Cooper GS, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. *JAMA Intern Med*.

2013;173(7):551-556. doi:10.1001/jamainternmed.2013.2908

205. Levin TR, Zhao W, Conell C, et al. Complications of colonoscopy in an integrated health care delivery system. *Ann Intern Med*. 2006;145(12):880-886. doi:10.7326/0003-4819-145-12-200612190-00004

206. Levin TR, Conell C, Shapiro JA, Chazan SG, Nadel MR, Selby JV. Complications of screening flexible sigmoidoscopy. *Gastroenterology*. 2002;123(6):1786-1792. doi:10.1053/gast.2002.37064

207. Chin M, Mendelson R, Edwards J, Foster N, Forbes G. Computed tomographic colonography: prevalence, nature, and clinical significance of extracolonic findings in a community screening program. *Am J Gastroenterol*. 2005;100(12):2771-2776. doi:10.1111/j.1572-0241.2005.00337.x

208. Macari M, Nevsky G, Bonavita J, Kim DC, Megibow AJ, Babb JS. CT colonography in senior versus nonsenior patients: extracolonic findings, recommendations for additional imaging, and polyp prevalence. *Radiology*. 2011;259(3):767-774. doi:10.1148/radiol.11102144

209. Cash BD, Riddle MS, Bhattacharya I, et al. CT colonography of a Medicare-aged population: outcomes observed in an analysis of more than 1400 patients. *AJR Am J Roentgenol*. 2012;199(1):W27-W34. doi:10.2214/AJR.11.7729

210. Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. *N Engl J Med*. 2007;357(14):1403-1412. doi:10.1056/NEJMoa070543

211. Kim DH, Pickhardt PJ, Hanson ME, Hinshaw JL. CT colonography: performance and program outcome measures in an older screening population. *Radiology*. 2010;254(2):493-500. doi:10.1148/radiol.09091478

212. Hoff G, Thiis-Evensen E, Grotmol T, Sauar J, Vatn MH, Moen IE. Do undesirable effects of screening affect all-cause mortality in flexible sigmoidoscopy programmes? experience from the Telemark Polyp Study 1983-1996. *Eur J Cancer Prev*. 2001;10(2):131-137. doi:10.1097/00008469-200104000-00003

213. Adeyemo A, Bannazadeh M, Riggs T, Shellnut J, Barkel D, Wasvary H. Does sedation type affect colonoscopy perforation rates? *Dis Colon Rectum*. 2014;57(1):110-114. doi:10.1097/DCR.0000000000000002

214. Flicker MS, Tsoukas AT, Hazra A, Dachman AH. Economic impact of extracolonic findings at computed tomographic colonography. *J Comput Assist Tomogr*. 2008;32(4):497-503. doi:10.1097/RCT.0b013e3181692091

215. Pox CP, Altenhofen L, Brenner H, Theilmeier A, Von Stillfried D, Schmiegel W. Efficacy of a nationwide screening colonoscopy program for colorectal cancer. *Gastroenterology*. 2012;142(7):1460-1467. doi:10.1053/j.gastro.2012.03.022

216. Kim JS, Kim BW, Kim JI, et al. Endoscopic clip closure versus surgery for the treatment of iatrogenic colon perforations developed during diagnostic colonoscopy: a review of 115,285 patients. *Surg Endosc*. 2013;27(2):501-504. doi:10.1007/s00464-012-2465-3

217. Lorenzo-Zúñiga V, Moreno de Vega V, Doménech E, Mañosa M, Planas R, Boix J. Endoscopist experience as a risk factor for colonoscopic complications. *Colorectal Dis*. 2010;12(10 online):e273-e277. doi:10.1111/j.1463-1318.2009.02146.x

218. Mansmann U, Crispin A, Henschel V, et al. Epidemiology and quality control of 245 000 outpatient colonoscopies. *Dtsch Arztebl Int*. 2008;105(24):434-440. doi:10.3238/arztebl.2008.0434

219. Ginnerup Pedersen B, Rosenkilde M, Christiansen TE, Laurberg S. Extracolonic findings at computed tomography colonography are a challenge. *Gut*. 2003;52(12):1744-1747. doi:10.1136/gut.52.12.1744

220. Gluecker TM, Johnson CD, Wilson LA, et al. Extracolonic findings at CT colonography: evaluation of prevalence and cost in a screening population. *Gastroenterology*. 2003;124(4):911-916. doi:10.1053/gast.2003.50158

221. Kim YS, Kim N, Kim SY, et al. Extracolonic findings in an asymptomatic screening population undergoing intravenous contrast-enhanced computed tomography colonography. *J Gastroenterol Hepatol*. 2008;23(7, pt 2):e49-e57. doi:10.1111/j.1440-1746.2007.05060.x

222. Veerappan GR, Ally MR, Choi JH, Pak JS, Maydonovitch C, Wong RK. Extracolonic findings on CT colonography increases yield of colorectal cancer screening. *AJR Am J Roentgenol*. 2010;195(3):677-686. doi:10.2214/AJR.09.3779

223. Pickhardt PJ, Kim DH, Taylor AJ, Gopal DV, Weber SM, Heise CP. Extracolonic tumors of the gastrointestinal tract detected incidentally at screening CT colonography. *Dis Colon Rectum*. 2007;50(1):56-63. doi:10.1007/s10350-006-0806-9

224. Durbin JM, Stroup SP, Altamar HO, L'esperance JO, Lacey DR, Auge BK. Genitourinary abnormalities in an asymptomatic screening population: findings on virtual colonoscopy. *Clin Nephrol*. 2012;77(3):204-210. doi:10.5414/CN107242

225. Dancourt V, Lejeune C, Lepage C, Gailliard MC, Meny B, Faivre J. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. *Eur J Cancer*. 2008;44(15):2254-2258. doi:10.1016/j.ejca.2008.06.041

226. Loffeld RJ, Engel A, Dekkers PE. Incidence and causes of colonoscopic perforations: a single-center case series. *Endoscopy*. 2011;43(3):240-242. doi:10.1055/s-0030-1255939

227. Kang HY, Kang HW, Kim SG, et al. Incidence and management of colonoscopic perforations in Korea. *Digestion*. 2008;78(4):218-223. doi:10.1159/000190811

228. Pickhardt PJ. Incidence of colonic perforation at CT colonography: review of existing data and implications for screening of asymptomatic adults. *Radiology*. 2006;239(2):313-316. doi:10.1148/radiol.2392052002

229. Ko CW, Riffle S, Shapiro JA, et al. Incidence of minor complications and time lost from normal activities after screening or surveillance colonoscopy. *Gastrointest Endosc*. 2007;65(4):648-656. doi:10.1016/j.gie.2006.06.020

230. Hara AK, Johnson CD, MacCarty RL, Welch TJ. Incidental extracolonic findings at CT colonography. *Radiology*. 2000;215(2):353-357. doi:10.1148/radiology.215.2.r00ap33353

231. Berhane C, Denning D. Incidental finding of colorectal cancer in screening colonoscopy and its cost effectiveness. *Am Surg*. 2009;75(8):699-703. doi:10.1177/000313480907500811

232. O'Connor SD, Pickhardt PJ, Kim DH, Oliva MR, Silverman SG. Incidental finding of renal masses at unenhanced CT: prevalence and analysis of features for guiding management. *AJR Am J Roentgenol*. 2011;197(1):139-145. doi:10.2214/AJR.10.5920

233. Suissa A, Bentur OS, Lachter J, et al. Outcome and complications of colonoscopy: a prospective multicenter study in northern Israel. *Diagn Ther Endosc*. 2012;2012:612542. doi:10.1155/2012/612542

234. Jain A, Falzarano J, Jain A, Decker R, Okubo G, Fujiwara D. Outcome of 5,000 flexible sigmoidoscopies done by nurse endoscopists for colorectal screening in asymptomatic patients. *Hawaii Med J*. 2002;61(6):118-120.

235. Viiala CH, Olynyk JK. Outcomes after 10 years of a community-based flexible sigmoidoscopy screening program for colorectal carcinoma. *Med J Aust*. 2007;187(5):274-277. doi:10.5694/j.1326-5377.2007.tb01241.x

236. Parente F, Boemo C, Ardizzoia A, et al. Outcomes and cost evaluation of the first two rounds of a colorectal cancer screening program based on immunochemical fecal occult blood test in northern Italy. *Endoscopy*. 2013;45(1):27-34.

237. Castro G, Azrak MF, Seeff LC, Royalty J. Outpatient colonoscopy complications in the CDC's Colorectal Cancer Screening Demonstration Program: a prospective analysis. *Cancer*. 2013;119(suppl 15):2849-2854. doi:10.1002/cncr.28159

238. Korman LY, Overholt BF, Box T, Winker CK. Perforation during colonoscopy in endoscopic ambulatory surgical centers. *Gastrointest Endosc*. 2003;58(4):554-557. doi:10.1067/S0016-5107(03)01890-X

239. Tam MS, Abbas MA. Perforation following colorectal endoscopy: what happens beyond the endoscopy suite? *Perm J*. 2013;17(2):17-21. doi:10.7812/TPP/12-095

240. Blotière PO, Weill A, Ricordeau P, Alla F, Allemand H. Perforations and haemorrhages after colonoscopy in 2010: a study based on comprehensive French health insurance data (SNIIRAM). *Clin Res Hepatol Gastroenterol*. 2014;38(1):112-117. doi:10.1016/j.clinre.2013.10.005

241. Strul H, Kariv R, Leshno M, et al. The prevalence rate and anatomic location of colorectal adenoma and cancer detected by colonoscopy in average-risk individuals aged 40-80 years. *Am J Gastroenterol*. 2006;101(2):255-262. doi:10.1111/j.1572-0241.2006.00430.x

242. Nelson DB, McQuaid KR, Bond JH, Lieberman DA, Weiss DG, Johnston TK. Procedural success and complications of large-scale screening colonoscopy. *Gastrointest Endosc*. 2002;55(3):307-314. doi:10.1067/mge.2002.121883

243. Crispin A, Birkner B, Munte A, Nusko G, Mansmann U. Process quality and incidence of acute complications in a series of more than 230,000 outpatient colonoscopies. *Endoscopy*. 2009;41(12):1018-1025. doi:10.1055/s-0029-1215214

244. Sieg A, Hachmoeller-Eisenbach U, Eisenbach T. Prospective evaluation of complications in outpatient GI endoscopy: a survey among German gastroenterologists. *Gastrointest Endosc*. 2001;53(6):620-627. doi:10.1067/mge.2001.114422

245. Xirasagar S, Hurley TG, Sros L, Hebert JR. Quality and safety of screening colonoscopies

performed by primary care physicians with standby specialist support. *Med Care*. 2010;48(8):703-709. doi:10.1097/MLR.0b013e3181e358a3

246. Bair D, Pham J, Seaton MB, Arya N, Pryce M, Seaton TL. The quality of screening colonoscopies in an office-based endoscopy clinic. *Can J Gastroenterol*. 2009;23(1):41-47. doi:10.1155/2009/831029

247. Quallick MR, Brown WR. Rectal perforation during colonoscopic retroflexion: a large, prospective experience in an academic center. *Gastrointest Endosc*. 2009;69(4):960-963. doi:10.1016/j.gie.2008.11.011

248. Dominitz JA, Baldwin LM, Green P, Kreuter WI, Ko CW. Regional variation in anesthesia assistance during outpatient colonoscopy is not associated with differences in polyp detection or complication rates. *Gastroenterology*. 2013;144(2):298-306. doi:10.1053/j.gastro.2012.10.038

249. Hamdani U, Naeem R, Haider F, et al. Risk factors for colonoscopic perforation: a population-based study of 80118 cases. *World J Gastroenterol*. 2013;19(23):3596-3601. doi:10.3748/wjg.v19.i23.3596

250. Bielawska B, Day AG, Lieberman DA, Hookey LC. Risk factors for early colonoscopic perforation include non-gastroenterologist endoscopists: a multivariable analysis. *Clin Gastroenterol Hepatol*. 2014;12(1):85-92. doi:10.1016/j.cgh.2013.06.030

251. Arora G, Mannalithara A, Singh G, Gerson LB, Triadafilopoulos G. Risk of perforation from a colonoscopy in adults: a large population-based study. *Gastrointest Endosc*. 2009;69(3, pt 2):654-664. doi:10.1016/j.gie.2008.09.008

252. Bokemeyer B, Bock H, Hüppe D, et al. Screening colonoscopy for colorectal cancer prevention: results from a German online registry on 269000 cases. *Eur J Gastroenterol Hepatol*. 2009;21(6):650-655. doi:10.1097/MEG.0b013e32830b8acf

253. An S, Lee KH, Kim YH, et al. Screening CT colonography in an asymptomatic average-risk Asian population: a 2-year experience in a single institution. *AJR Am J Roentgenol*. 2008;191(3):W100-W106. doi:10.2214/AJR.07.3367

254. Wallace MB, Kemp JA, Meyer F, et al. Screening for colorectal cancer with flexible sigmoidoscopy by nonphysician endoscopists. *Am J Med*. 1999;107(3):214-218. doi:10.1016/S0002-9343(99)00225-9

255. Ko CW, Riffle S, Michaels L, et al. Serious complications within 30 days of screening and surveillance colonoscopy are uncommon. *Clin Gastroenterol Hepatol*. 2010;8(2):166-173. doi:10.1016/j.cgh.2009.10.007

256. Ho JM, Gruneir A, Fischer HD, et al. Serious events in older Ontario residents receiving bowel preparations for outpatient colonoscopy with various comorbidity profiles: a descriptive, population-based study. *Can J Gastroenterol*. 2012;26(7):436-440. doi:10.1155/2012/238387

257. Pickhardt PJ, Boyce CJ, Kim DH, Hinshaw LJ, Taylor AJ, Winter TC. Should small sliding hiatal hernias be reported at CT colonography? *AJR Am J Roentgenol*. 2011;196(4):W400-W404. doi:10.2214/AJR.10.5392

258. Layton JB, Klemmer PJ, Christiansen CF, et al. Sodium phosphate does not increase risk for acute kidney injury after routine colonoscopy, compared with polyethylene glycol. *Clin Gastroenterol Hepatol*. 2014;12(9):1514-21. doi:10.1016/j.cgh.2014.01.034

259. Pickhardt PJ, Hanson ME, Vanness DJ, et al. Unsuspected extracolonic findings at screening CT colonography: clinical and economic impact. *Radiology*. 2008;249(1):151-159. doi:10.1148/radiol.2491072148

260. Atkin WS, Hart A, Edwards R, et al. Uptake, yield of neoplasia, and adverse effects of flexible sigmoidoscopy screening. *Gut*. 1998;42(4):560-565. doi:10.1136/gut.42.4.560

261. Basson MD, Persinger D, Newman WP. Association of colonoscopy with risk of appendicitis. *JAMA Surg*. 2018;153(1):90-91. doi:10.1001/jamasurg.2017.3790

262. Kobiela J, Spychalski P, Wieszczy P, et al. Mortality and rate of hospitalization in a colonoscopy screening program from a randomized health services study. *Clin Gastroenterol Hepatol*. 2020;18(7):1501-1508.

263. Grossberg LB, Papamichael K, Leffler DA, Sawhney MS, Feuerstein JD. Patients over age 75 are at increased risk of emergency department visit and hospitalization following colonoscopy. *Dig Dis Sci*. 2020;65(7):1964-1970.

264. Penz D, Ferlitsch A, Waldmann E, et al. Impact of adenoma detection rate on detection of advanced adenomas and endoscopic adverse events in a study of over 200,000 screening colonoscopies. *Gastrointest Endosc*. 2020;91(1):135-141. doi:10.1016/j.gie.2019.08.038

265. Chukmaitov A, Dahman B, Bradley CJ. Outpatient facility volume, facility type, and the risk of serious colonoscopy-related adverse events in patients with comorbid conditions: a population-based study. *Int J Colorectal Dis*. 2019;34(7):1203-1210. doi:10.1007/s00384-019-03304-3

266. Thulin T, Hammar U, Ekbom A, Hultcrantz R, Forsberg AM. Perforations and bleeding in a population-based cohort of all registered colonoscopies in Sweden from 2001 to 2013. *United European Gastroenterol J*. 2019;7(1):130-137. doi:10.1177/2050640618809782

267. Pooler BD, Kim DH, Pickhardt PJ. Indeterminate but likely unimportant extracolonic findings at screening CT colonography (C-RADS Category E3): incidence and outcomes data from a clinical screening program. *AJR Am J Roentgenol*. 2016;207(5):996-1001. doi:10.2214/AJR.16.16275

268. Derbyshire E, Hungin P, Nickerson C, Rutter MD. Post-polypectomy bleeding in the English National Health Service Bowel Cancer Screening Programme. *Endoscopy*. 2017;49(9):899-908. doi:10.1055/s-0043-113442

269. Senore C, Ederle A, Fantin A, et al. Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting. *J Med Screen*. 2011;18(3):128-134. doi:10.1258/jms.2011.010135

270. Regula J, Polkowski M. CT colonography versus colonoscopy for the detection of advanced neoplasia. *N Engl J Med*. 2008;358(1):88-89. doi:10.1056/NEJMc073084

271. Pickhardt PJ, Kim DH, Robbins JB. Flat (nonpolypoid) colorectal lesions identified at CT colonography in a U.S. screening population. *Acad Radiol*. 2010;17(6):784-790. doi:10.1016/j.acra.2010.01.010

272. Hoff G, Sauar J, Vatn MH, et al. Polypectomy of adenomas in the prevention of colorectal cancer: 10 years' follow-up of the Telemark Polyp Study I: a prospective, controlled population study. *Scand J Gastroenterol*. 1996;31(10):1006-1010. doi:10.3109/00365529609003121

273. Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer: Telemark Polyp Study I. *Scand J Gastroenterol*. 1999;34(4):414-420. doi:10.1080/00365529750026443

274. Zalis ME, Barish MA, Choi JR, et al; Working Group on Virtual Colonoscopy. CT colonography reporting and data system: a consensus proposal. *Radiology*. 2005;236(1):3-9. doi:10.1148/radiol.2361041926

275. Lord SJ, Irwig L, Simes RJ. When is measuring sensitivity and specificity sufficient to evaluate a diagnostic test, and when do we need randomized trials? *Ann Intern Med*. 2006;144(11):850-855. doi:10.7326/0003-4819-144-11-200606060-00011

276. Liles E, Coronado G, Perrin N, et al. Uptake of a colorectal cancer screening blood test is higher than of a fecal test offered in clinic: a randomized trial. *Cancer Treat Res Comm*. 2017;10:27-31. doi:10.1016/j.ctarc.2016.12.004.

277. White A, Thompson TD, White MC, et al. Cancer screening test use—United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(8):201-206. doi:10.15585/mmwr.mm6608a1

278. Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. *Screening for Colorectal Cancer: A Systematic Review for the US Preventive Services Task Force*. Agency for Healthcare Research and Quality; 2021.

279. Usher-Smith JA, Walter FM, Emery JD, Win AK, Griffin SJ. Risk prediction models for colorectal cancer: a systematic review. *Cancer Prev Res (Phila)*. 2016;9(1):13-26. doi:10.1158/1940-6207.CAPR-15-0274

280. Peng Z, Zhu W, Dai J, Ju F. MicroRNA-200 as potential diagnostic markers for colorectal cancer: meta-analysis and experimental validation. *Cell Mol Biol (Noisy-le-grand)*. 2018;64(6):77-85. doi:10.14715/cmb/2018.64.6.14

281. Usher-Smith JA, Harshfield A, Saunders CL, et al. External validation of risk prediction models for incident colorectal cancer using UK Biobank. *Br J Cancer*. 2018;118(5):750-759. doi:10.1038/bjc.2017.463

282. Smith T, Muller DC, Moons KGM, et al. Comparison of prognostic models to predict the occurrence of colorectal cancer in asymptomatic individuals: a systematic literature review and external validation in the EPIC and UK Biobank prospective cohort studies. *Gut*. 2019;68(4):672-683. doi:10.1136/gutjnl-2017-315730

283. Win AK, Macinnis RJ, Hopper JL, Jenkins MA. Risk prediction models for colorectal cancer: a review. *Cancer Epidemiol Biomarkers Prev*. 2012;21(3):398-410. doi:10.1158/1055-9965.EPI-11-0771